The Journal of Pediatrics

VOL. 55 AUGUST, 1959 NO. 2

THE PHASES OF "TRANSITIONAL DISTRESS" OCCURRING IN NEONATES IN ASSOCIATION WITH PROLONGED POSTNATAL UMBILICAL CORD PULSATIONS

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IN a study of the behavior of infants with a history of fetal distress it has been previously noted that the recovery process is a sequential one and takes place at various rates.[1] More recent experience with distressed infants revealed that certain of these infants show disturbances in the closure of umbilical vessels after birth.[2]

The umbilical arteries normally cease to pulsate within a short period after the infant has been delivered. The average time required for the cessation of pulsation has been observed to be 10 minutes by Windle,[3] the range to be 1 to 15 minutes by Haselhorst and Trautvetter,[4] and the upper limit of normal to be 30 minutes by Haselhorst and Allmeling.[4]

While ligation of the umbilical cord immediately after birth is a tradition in modern obstetrics, the danger of hemorrhage from cords left unligated is not great[5]; Barclay quotes two large series of deliveries in which umbilical cords were routinely left unligated. Rachmanow[6] considered cord ligation to be a therapeutic measure reserved for pathologic and exceptional cases and necessary only in 10 to 20 per cent of births. Diminished contractility of the cord vessels has been noted in weak, premature, and undernourished infants; in such cases there is increased danger of hemorrhage from the divided cord. The musculature may relax after initial closure.[7]

The closure of the umbilical arteries is brought about by the contraction of smooth muscle in the wall of the vessel in response to a stimulus or stimuli.[4] Nervous tissue has not been demonstrated in these vessels.[8] Local contraction has been shown to follow cooling, mechanical compression, electrical stimulation, the presence of oxygen in perfusion fluids, and high concentrations of epinephrine. Dilation of these vessels is favored by warmth and by perfusion with carbon dioxide or with nitrogen-saturated solutions.[4]

This paper describes the clinical courses of 41 infants with prolonged pulsations of the umbilical arteries

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Supported by the Memo Set Fund of Battelstein's, Inc., Houston; the Houston Heart Association, Grant 603-7-58; and the USPH Grant B-1724 #511.562.

after delivery and presents a theory to explain the clinical behavior of the infants as well as the pulsations of their cords.

SUBJECTS AND METHODS

The 41 infants reported in this study were seen over the period of a year in the newborn infant nurseries of Jefferson Davis, Hermann, and St. Luke's Hospitals in Houston. Nurses were requested to observe and to palpate the cord at the time of admission to the nursery. Resident physicians were requested to palpate all umbilical cords at the time of the initial examination of the infant. If pulsations were noted, the infant was kept under close observation by us for the remainder of his hospital stay. Since any disturbance of the infant appeared to alter clinical symptomatology, procedures and handling were kept to a minimum.

RESULTS

Character of Pulsation.—In the majority of instances it was not possible to determine whether the pulsations were arterial or venous. In those infants in whom it was possible to palpate the veins and arteries separately, the pulsations were present only over the arteries. When pulsating cords were severed, blood was seen to spurt from the arteries. Pulsations were considered to be *major* when they were both visible and palpable and to be *minor* when palpable only. The rate of pulsation was found to be synchronous with the heart rate, unless the force of pulsation was diminishing prior to cessation. A minor pulsation could be temporarily or completely terminated by compression of the cord.

Forty-one infants manifested prolonged pulsation of the cord after delivery. The mean duration of cord pulsation was 5 hours, with a range of from 40 minutes to 13 hours after birth. Major or visible pulsations were noted in 10 of the 41 infants. In 5 infants the pulsations progressed under observations from minor to major and once again to minor prior to complete cessation. Three infants with quiescent cords developed cord pulsations concomitant with respiratory distress in the first few hours of life.

TABLE I. MATERNAL COMPLICATIONS*

ANTE PARTUM	NUMBER	INTRAPARTUM	NUMBER
Anemia	8	Premature rupture of the membranes	4
Obesity	6	Abnormal presentation	4
Toxemia	7	Twin delivery	3
Diabetes mellitus	4	Precipitate labor	7
Polyhydramnios	4	Uterine inertia	3
Infection	4	Prolapsed cord	2
Acute blood loss	3	Shoulder dystocia	2
Late pregnancy bleeding	5	Hypotensive episode	3
Psychosis	1		
Cervical neoplasm	1		
Status asthmaticus	1		

*Premature labor not included.

Ante-partum and Intrapartum Histories.—Of the infants manifesting prolonged pulsation, 14 (34 per cent) were prematurely born. A high rate

of maternal ante-partum and intra-partum complications were present (Tables I and II). Only one mother and infant pair could fulfill Eastman's and De Leon's criteria[9] for normal pregnancy and delivery. Twelve (20 per cent) of the infants were delivered by cesarean section; of these, 7 were emergency procedures and 5, elective procedures. Thirty (73 per cent) of the infants had a history of either fetal distress before delivery or difficulty in establishing respirations at birth. Twenty two of the above 30 (or 53 per cent of the total) had histories of fetal distress (meconium staining of the amniotic fluid or sustained bradycardia) prior to or during delivery; 21 (or 51 per cent of the total) were considered to be in poor condition (Apgar[10] score of 5 or less) during the first 1 to 2 minutes after delivery. All infants considered in poor condition at birth received some form of resuscitation.

Clinical Behavior.—Three of the infants had no recorded difficulty after delivery, 8 had transient symptomatology, and 30 developed significant disease. Sixteen of these 30 had difficulty continuing from birth, 8 had the onset between birth and 1 hour of age, and 4 between 1 and 2 hours of age. The latest onset (between 2 and 6 hours) occurred in 2 infants whose predominant manifestation was hemorrhage from the cord.

Five infants expired during the first 11 hours of life. Two additional infants survived the initial illness and succumbed to hospital-acquired infections during the second half of the neonatal period.

The infants with prolonged umbilical cord pulsations after delivery are

TABLE II

GROUP	NO. OF PATIENTS	PREMATURE INFANTS	COMPLICATIONS OF DELIVERY			CESAREAN SECTION		FETAL DISTRESS PRIOR TO DELIVERY	CONDITION AT BIRTH			DEATHS
			NONE	ANTE PARTUM	INTRA-PARTUM	TOTAL	EMERGENCY		GOOD	FAIR	POOR	
I	11	4	2	6	5	3	2	4	7	1	3	0
II	4	1	0	4	4	0	0	3	1	0	3	1
III	17	7	3	9	8	6	4	12	6	0	11	2
IV	6	2	0	6	4	2	1	3	1	1	4	2
V	3	0	1	1	0	1	0	0	3	0	0	0
Totals	41	14	6	26	21	12	7	22	18	2	21	5
Percentages	100	34	15	63	51	29	17	54	44	5	51	12.5

divided into five main groups on the basis of predominant clinical symptomatology (Table III).

Group I.—

No observed disease (3 cases):

Transient symptomatology without a definite clinical pattern (8 cases): Umbilical cord pulsations were noted to be present from the time of birth in 7 infants included in Group I. The exact time of onset of pulsation in the remaining 4 infants was not known. The average time of cessation of pulsation was 5 hours (range 1½ to 9 hours).

The neonatal period of 3 infants was completely uneventful, while 8 had transient symptomatology. Of the latter 8 infants, 6 showed one or more of the following symptoms during the period of cord pulsation: excessive oral mucus (1), lower sternal retraction (1), lethargy and depressed reflexes* (2), increased respiratory rate of 70 per minute (1), and liver enlargement (1). After the cord ceased to pulsate, 7 of the 8 infants showed one or more of the following symptoms: tremulousness (3), excessive, irritable crying (1), hypertonus (1), high-pitched cry (1), and tachypnea (1). Three of the infants in this group developed jaundice between the second and third day of life (1, incompatibility and 2, unknown). Initial roentgenograms on 2 infants showed neonatal atelectasis. All infants were in excellent condition by 12 hours of life and all survived the neonatal period (see appendix for case summary).

Group II. Pulmonary Manifestations Associated With Apparent Mechanical Obstruction (4 Cases).—This category consists of infants whose primary distress was due to mechanical interference with ventilation. All 4 infants were in difficulty from the time of birth.

The first infant had laryngeal stenosis secondary to a tumor mass. This infant showed stridor, deep violent retraction on inspiration, poor air exchange bilaterally, severe cyanosis, and minor cord pulsation. During the first 6 hours after birth, the infant developed progressive cyanosis, inactivity, and diminishing reflex response. When the obstruction was bypassed with an endotracheal catheter, the infant took one breath, became pink, and ceased to breathe for a few seconds. The cord immediately ceased to pulsate. Following the brief period of apnea, respirations were at first extremely shallow and rapid. Ten minutes following intubation, the infant appeared to be normal.

TABLE III

	INFANTS WITH UMBILICAL CORD PULSATIONS	NUMBER OF INFANTS
Group I	No observed disease	3
	Transient symptomatology without a definite clinical pattern	8
Group II	Pulmonary manifestations associated with apparent mechanical obstruction	4
Group III	Cardiopulmonary manifestations	17
Group IV	Neurologic manifestations	6
Group V	Cord hemorrhage	3
	Total	41

*Sucking, root, Moro, hand grasp, toe grasp, withdrawal, and deep tendon reflexes.

The second infant had marked abdominal distention from birth and was noted to have a pulsating cord at 2 hours of age. The cord ceased to pulsate at 4 hours and the abdominal distention subsided by 9 hours of age.

The third infant had a tension pneumothorax associated with severe respiratory distress. The infant expired and at autopsy was found to have massive collapse of the lungs and multiple genitourinary anomalies.

The fourth infant had a left-sided tension pneumothorax and pneumomediastinum. Cord pulsations ceased within 5 minutes after the obstruction was relieved by aspiration of 30 c.c. of air.

Group III. Cardiopulmonary Manifestations (17 Cases).—This category is the largest of the series and includes infants exhibiting cardiopulmonary distress along with major or minor cord pulsations. A sequential development of three phases of respiration occurred in the 15 surviving infants and incompletely in 2 infants who expired.

Since the clinical behavior reported here is to be compared later in the text with the behavior of patients recovering from anesthetic or anoxic depression, the numerical designations of the phases are in keeping with the order generally used to describe the stages of anesthetic or anoxic depression. The highest number is given to the phase corresponding to the stage of deepest depression. (see Table IV).

Phase 3: At birth 11 infants manifested either apnea or gasping respiration. Following this, the infants developed labored respiration. This type of respiration was observed in all infants in this group and was characterized by continuous or recurrent flaring of the alae nasae, subcostal retraction, expiratory grunting, cyanosis, and deep regular respiration at a normal or a moderately increasing rate. The heart rate was normal and regular; the heart tones were loud and clear, with an accentuated pulmonic second sound (P_2) in 15 of the 17 infants. The two exceptions were considered to be in congestive failure from the time of birth. The eyelids were closed, and the infants remained inactive and disinclined to suck. In the upper portion of this phase the cry was more vigorous and the Moro reflex obtainable. The average duration of this phase in surviving infants was 5 hours, with a range of from 1 to 13 hours.

The complications which occurred during the course of this phase were: hyaline membrane disease (1), atelectasis (4), and congestive failure (3).

Phase 2: This phase followed or appeared coincidentally with the cessation of cord pulsation. Respiration changed from a labored type to a rapid, regular respiration, with inspiration equal to or longer than expiration. In some infants respiration was "pantlike" and in others, shallow and noiseless. The heart rate tended to increase transiently. The increased P_2 disappeared and the sounds became less clear and forceful. The infants opened their eyes and began to yawn, stretch, and suck their fingers. Some were able to tolerate oral feedings well in spite of the rapid respiration. Gradually the rate of respiration declined and irregularities appeared. Tremors of the extremities and hyperirritability were present toward the end of this phase. The reflexes were normal to exaggerated. On feeding or handling or rapid reduction of oxygen the infants returned briefly to Phase 3.

TABLE IV

ANESTHESIA		ANOXIA	AUTONOMIC NERVOUS SYSTEM (HIMWICH[16])	TRANSITIONAL DISTRESS OF THE NEONATE		COMPLICATIONS	FACTORS IN NEONATE MODIFYING SYMPTOMATOLOGY
STAGES OF ANESTHESIA (BURSTEIN[15])	SITE OF ANESTHETIC DEPRESSION (HIMWICH[16])	PHASES OF ACUTE ANOXIA (HIMWICH[16])		CARDIOPULMONARY PHASES	NEUROLOGIC PHASES		
I Analgesia	Slight depression of cortex to moderate depression of cortex	First Phase Depression of cortical and cerebellar activity					Minimal cortical activity
II Excitement	Predominant control by subcortex	Second Phase Release of subcortico-diencephalic region	Varies with stimuli	Phase 1 Normal lability or periodic breathing Physiologic lability of heart rate	Phase 1 Normal activity Normal reflexes	Jaundice	Cortical activity diminished to absent with immaturity
III Surgical Plane 1	Moderate depression of subcortex		Predominantly sympathetic	Phase 2 Decreasing respiratory rate Transient increase in heart rate Rapid regular respirations	Phase 2 Upper Reflexes exaggerated Increased tonus Lower Hyperactivity and tremors Abdominal distention Chewing and smacking Returning reflexes Open eyes, anxious expression	Jaundice Seizures and/or apnea Vomiting Cord hemorrhage	Diminished intercostal muscle activity

Plane 2	Predominant control by midbrain	Third Phase Release of midbrain	Parasympathetic	Phase 3 Respiration, increased rate and less labored Normal heart rate	Phase 3 Hyperperistalsis Diminished reflexes Inactivity Poor response to stimulation		Diminished intercostal muscle activity
Plane 3	Moderate depression of midbrain	Fourth Phase Release of upper medulla oblongata	Sympathetic or parasympathetic	Grunting, labored respiration		Congestive failure	
Plane 4	"Stage IV," moderate depression of pons	Fifth Phase Release of lower medulla oblongata	Maximal parasympathetic	Gasping respiration Cyanosis Slowing heart rate Apnea neonatorum	Absent reflexes Hypotonus Unresponsive to stimulation	Hyaline membrane disease Atelectasis	
IV	"Stage V," medullary failure			Death	Death		

On the left portion of Table IV correlations are made between the planes of anesthesia, the central site of anesthetic action, the phases of induced anoxia, and the predominant autonomic activity at each level of cerebral depression. On the right the signs and symptoms observed in these distressed infants (transitional distress) have been divided into phases under two main groupings, cardiopulmonary and neurologic. These phases have also been correlated with the stages of anesthetic and anoxic depression and the autonomic predominance at each level. Complications occurring during each phase have been listed. In the last column are noted neonatal factors which may account for differences in the response of the adult and of the infant to cerebral depression.

Phase 1: In Phase 1 respirations continued to decrease in rate. The normally labile or periodic breathing of the neonate was gradually attained. Tremors, tremulousness, and hyperirritability frequently continued into the lower portions of this phase. Jaundice occurred in either upper Phase 2 or Phase 1 (4 cases) (for case histories, see appendix).

Group IV. Neurologic Manifestations (6 Cases).—In this group prolonged and major pulsation of the umbilical cord was associated with respiratory distress and signs of predominant nervous system involvement. Two of the infants in this group were prematurely born. All pregnancies had complications prior to as well as during delivery. Four infants were apneic at birth, and all had difficulty within an hour of birth. The clinical sequence occurred in three steps:

Phase 3: All infants had excessive oral mucus. They were cyanotic and breathed in a labored, irregular manner at a normal or moderately increasing rate. The cry was weak and poorly maintained, and the eyelids were closed. The infants were hypotonic, had diminished reflexes, and demonstrated slow or absent response to stimulation. Hyperperistalsis was present in the upper portions of this phase.

Phase 2: Lower. In the lower portion of Phase 2 the infants remained cyanotic out of oxygen. Respiration as in Phase 3 was irregular with an over-all increase in rate. Interspersed with rapid, shallow respirations were periods of apnea, diaphragmatic tremors, and retractions. At the beginning of this phase the infants exhibited a marked, often abrupt, change in behavior. The eyelids opened and the expression became one of staring or of anxiety. Chewing, smacking, and grimacing movements were frequent. After spontaneous activity returned, the infants developed tremors, jerks, and bursts of movement involving all extremities.

Upper. In the upper portion of Phase 2 respiration decreased in rate and less oxygen was required. The skin appeared mottled and dermatographia could be elicited. At intervals apnea with or without associated extensor-flexor movements occurred. The reflexes were exaggerated and hypertonus was present. The suck was incoordinate and the gag reflex, hypersensitive. Vomiting was noted with or sometimes without oral feeding. Three infants showed clearly defined generalized seizures.

Phase 1: In Phase 1 the infant gradually assumed the appearance of normal activity and behavior.

Six infants were included in this group. The most severely involved infant never established spontaneous respiration and remained atonic and areflexic for her 1 hour of life. A second infant remained in Phase 3 for the entire 9 hours of life. The third infant (Case 1) progressed from lower Phase 2 to Phase 1 without the marked neurologic symptoms of upper Phase 2. The clinical behavior of the remaining 3 infants followed the complete sequence of the phases as noted above. The appearance of normalcy was reached at 7, 10, and 18 days of life, respectively. Twenty-six infants included in other groups had neurologic symptoms in the same general sequence but the clinical

picture was either brief or dominated by other clinical symptomatology (for case summaries, see appendix).

Group V. Cord Hemorrhage (3 Cases).—The three infants included in this group had hemorrhage from the cord as their major finding. Hemorrhage was associated with cord pulsations, apprehension and tremors, and continued despite repeated ligations with umbilical cord tape.

The first infant had continuous bleeding from the umbilical arteries between the fourth and sixth hours of life. The second had a sudden massive cord hemorrhage at 6 hours of age followed by clinical signs of blood loss (pallor, tachycardia, and anemia). The site of bleeding was noted to be arterial.

The third infant, a malnourished term baby, had continuous oozing of blood from the cord between the first and twelfth hour of life. The infant's color was slightly dusky in room air. In oxygen the fingernail beds, ears, and lips, became vivid red in color and the baby appeared tremulous, apprehensive, and irritable. The hemoglobin was 18 Gm. per cent. A Grade 3 systolic murmur was heard over the precordium during the first 24 hours of life. The infant has been followed in the outpatient department for one year and has shown no evidence of congenital heart disease.

(Three additional infants had hemorrhage from the cord. They have been placed in other groups in accordance with the predominant symptomatology.)

DEATHS

There were 5 deaths in this series. All pregnancies were complicated and fetal distress was evident in 4 of these infants. All had difficulty with the onset of respiration and all continued to show distress from birth until death. The duration of life was short, with an average of 7 hours and a range of from 1 to 11 hours. Major cord pulsations were noted in 4 of the 5 infants. Prior to death, pulsations ceased entirely.

Three infants were born at term. The causes of these deaths were: severe anemia following Rh sensitization, congenital pneumonia, and multiple genitourinary anomalies associated with tension pneumothorax. The later two diagnoses were made at autopsy. All expired in Phase 3.

The two premature infant deaths were strikingly similar. Both were delivered by emergency cesarean section for fetal distress. One pregnancy was complicated by diabetes mellitus and the other by severe maternal blood loss. These infants were also in Phase 3 prior to death. Neither infant developed the rapid regular respiration and signs of sympathetic predominance characteristic of Phase 2. At postmortem examination hyaline membranes were present in the lungs of both infants and intraventricular hemorrhage in one. These cases resemble those previously described by Miller and colleagues.[11]

MANAGEMENT

Since the phenomenon under observation, the pulsating cord, was a physical sign of uncertain significance, no planned method of management was instituted at the beginning of the study. During the study, however, the following principles of management evolved and were individualized for each infant.

Procedures and manipulations were kept to a minimum as these appeared not only to alter the symptomatology under observation but also to affect the more distressed infants adversely.

Oxygen was used liberally in concentrations above 40 per cent during Phase 3 and with cyanosis in early Phase 2. Parenteral glucose solutions were given to selected infants in Phase 3 and during periods of preconvulsive and convulsive activity in Phase 2. Oral feedings appeared to become hazardous as evidences of neural excitation appeared in this phase. Intravenous glucose served the twofold purpose of nutrition and of mild sedation.

Anticonvulsant therapy with Dilantin* and Mebaral† was employed in the treatment of seizures and of protracted vomiting. Periodic flexor-extensor movements associated with apnea were considered to be specific seizures. In selected infants with extreme degrees of neural excitation sedation was given early for the possible prevention of frank seizures. (This type of therapy is currently being evaluated in a controlled study.)

DISCUSSION

Forty-one infants whose umbilical vessels continued to pulsate for periods of 40 minutes or longer after birth have been followed clinically during the neonatal period. As a group, these infants had high morbidity and mortality rates. Fifty-one per cent were given a rating of "poor" at delivery (see Table II) and 93 per cent had some evidence of disturbance in adaption to extrauterine life. With one exception, all of the babies had at least one of the following: fetal distress, difficulty in onset of respiration, or symptomatology during the first 6 hours of life. Thus, in the series of infants described here persistence of pulsation over the umbilical cord appears to be associated with difficulty in the transition from intrauterine to extrauterine life.

This view is consistent with reports on this subject in the literature. Bondi (quoted by Barclay),[4] in 1905, noted an association between delayed onset of respiration after birth and a longer period of umbilical artery pulsation. Krafka[7] stated that in weak, premature, or undernourished infants the umbilical arteries may have diminished contractility. Chown and Bowman[12] have described vigorous pulsations of the umbilical vessels in infants with severe hemolytic disease.

Each infant in this series was carefully examined. An attempt was made to find a lesion or disorder in the infant which could be held responsible for his current symptomatology. Only in a minority of infants (8 of 41) were specific clinical entities found. These included laryngeal stenosis, pneumothorax, severe hemolytic anemia, bronchopneumonia, severe abdominal distention, and congestive failure. These entities may be classified as intrinsic[13] or intrafetal. All interfered with oxygenation of the infant after birth, regardless of their presence or effects on the infant during intrauterine life.

In the majority of infants, however, the physical examinations performed when the cord pulsations were first noted were singularly unrevealing. No specific clinical entity which might explain current symptomatology could be found in 30 infants. It was necessary therefore to look beyond the baby to his intrauterine environment

*Dilantin sodium is manufactured by Parke, Davis & Co.

†Mebaral is manufactured by the Winthrop Laboratories.

in order to account for his extrauterine problems. The sources of difficulty in these infants may be classified as extrinsic[13] or extrafetal since they originated outside the infant. Upon delivery, the infant was separated from further adverse intrauterine influences and his immediate neonatal problem became one of recovery as well as of transition.

Regardless of the presenting symptomatology, infants with prolonged pulsation of the umbilical vessels showed certain similarities in clinical behavior and followed a definite pattern of symptomatology during the first hours or days of life. The symptomatology was largely cardiopulmonary and neurologic in type and developed in a series of three phases. These are summarized in Table IV under the heading "transitional distress."

In Phase 3 respiration progresses from slow, gasping respiration to labored grunting and finally to a more rapid rate, with or without retraction. At the same time the heart rate progresses from a bradycardia to a normal rate. The reflexes (Moro, suck, withdrawal, grasp, etc.) are first diminished, tone is poor, and parasympathetic effects predominate at the level of greatest depression.

In Phase 2 the respiration is rapid, shallow, and regular and the heart rate transiently increased. Reflexes return and autonomic activity is predominantly sympathetic. As the rapid respiratory rate begins to decline, the patient may either progress directly to Phase 1 or exhibit evidences of neural excitation.

In Phase 1 respiration and cardiac activity gradually return to the lability characteristic of the neonate. Sympathetic predominance gradually declines and the neurologic behavior approaches the normal.

Infants with extrinsic disease who appeared to be improving clinically followed a sequence of phases from 3 to 2 to 1; infants who appeared to be deteriorating clinically followed the same sequence of symptomatology in reverse order, i.e., phases 1 to 2 to 3. Infants with intrinsic disease and superimposed hypoxia followed a similar sequence as they were improving or deteriorating clinically.

The sequence of clinical behavior seen in infants with prolonged pulsations of the umbilical vessels closely resembles the clinical behavior of patients who are recovering from deep anesthesia,[15, 16] hypoglycemia,[14, 16] anoxia,[16-19] narcosis,[16] and cardiac arrest.[20]

The symptomatology in these depressions follows a sequence of stages or phases and is well documented in the literature. In general, these insults bring about a descending depression of the neuraxis in which the more recent portions of the brain phylogenetically are affected before the older, less metabolically active regions. With descending depression, the clinical behavior of the patient reflects a successive depression of the cerebral hemispheres, basal ganglia, diencephalon, midbrain, and medulla as each layer is functionally eliminated and the lower layer is released from the inhibition of the upper layer. When the recovery of the neuraxis takes place, a similar sequence of symptomatology is followed, but in a reverse order.[16] If factors peculiar to the newborn infant (i.e., the relative metabolic inactivity of the cortex, the high

level of metabolic activity in the brain stem of the more immature subject,[16] and a diminished intercostal muscle activity) are considered, the pattern of clinical behavior described in this paper closely resembles the clinical behavior seen in older patients recovering from narcosis, deep anesthesia, or asphyxia.

of an intrauterine insult is also suggested by the close relationship between birth and onset of symptomatology.

A schematic representation of the phases of intrauterine depression and extrauterine recovery is presented in Fig. 1. The cardiopulmonary and neurologic phases are combined in this schema.

TABLE V. THE DURATION OF CORD PULSATION AND PHASES OF "TRANSITIONAL DISTRESS" IN SURVIVING INFANTS OF GROUPS I, III, AND IV

GROUP	NUMBER OF PATIENTS	CESSATION OF CORD PULSATION (HOURS)	END OF PHASE 3 (HOURS)	END OF PHASE 2 (HOURS AND DAYS)
I Transient symptomatology	8	5 (1 to 9)	No symptoms noted after 1½ hours	6 hours (1 hour to 5 days)
III Cardiopulmonary manifestations	15	5 (1 to 13)	5 (1 to 14)	24 hours (4 hours to 7 days)
IV Neurologic manifestations	4	4 (1 to 10)	6 (1 to 14)	6 days (5 to 18 days)

The values given are expressed as the median and the range.

Since the sequence of phases (1 to 2 to 3) seen in infants deteriorating clinically is similar to that seen in progressive cerebral depression and since the sequence in improving infants (3 to 2 to 1) resembles that of recovery from depression, it may be postulated that infants undergoing these sequences are undergoing respectively, depression or recovery of the neuraxis.

Since the majority of infants followed the pattern of recovery from the time of birth, it may be assumed that a cerebral depression occurred prior to the onset of recovery, i.e., during intrauterine life. The maternal histories and the histories of labor and delivery support this assumption since 86 per cent of these pregnancies and deliveries had complicating factors and since 73 per cent of the infants had either fetal distress before delivery, or were in poor condition at the time of birth (Tables I and II). The presence

The past histories of these infants suggest that the cerebral depression postulated here represents a summation of effects occurring during the course of an abnormal pregnancy, labor, or delivery. James and coworkers[21] have emphasized the depressive effects of asphyxia and agents used for anesthesia and analgesia. It is possible that the effects of asphyxia and/or depressant drugs may have been potentiated by the direct or indirect effects of the great variety of agents used during pregnancy and labor in this series, i.e., oxytocics, antihypertensives, pressor agents, stimulants, diuretics, antihistaminics, antibiotics, and ataractics. Drugs which modify the function of the autonomic nervous system or alter the internal environment significantly may perhaps influence the response of the infant to asphyxia or alter his ability to recover from a prior depression.

Of the 38 infants with symptomatology, 20 began the neonatal period in Phase 3 and 18 in Phase 2. Twelve of the Phase 2 infants continued to improve while 6 regressed to Phase 3 within 2 hours of life. It is of interest to note that 5 of the latter infants were premature, 5 were born by cesarean section, 4 had fetal distress prior to delivery, and 3 were infants of diabetic mothers.

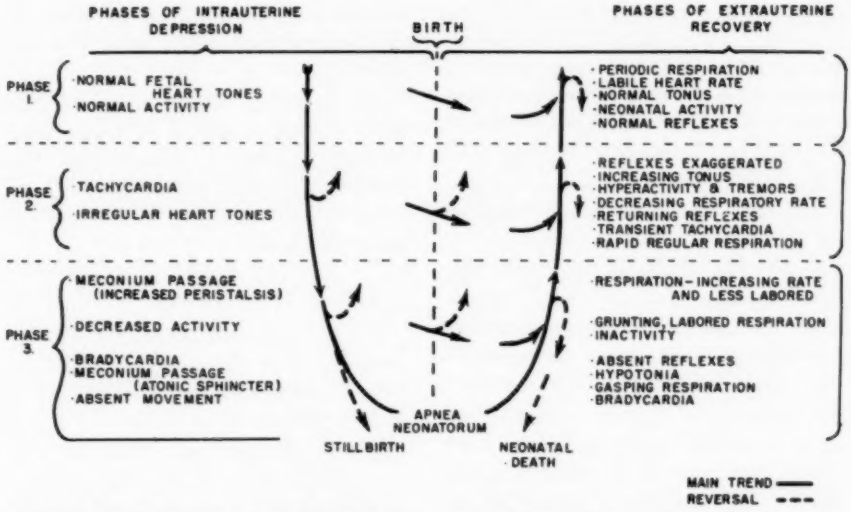

Fig. 1.—*A theoretical representation of the phases of cerebral depression and recovery in the fetus and neonate.* The signs and symptoms observed in these depressed infants have been grouped in schematic form to correlate with a theoretical depression of the fetus and recovery of the neonate.

The ages of the infants at the time of cessation of cord pulsation and at the end of Phase 3 and Phase 2 are given in Table V. The median period of cord pulsation is similar in all groups. The duration of Phase 2 is considerably longer in infants whose symptomatology was predominantly neurologic in comparison with those whose symptoms were predominantly cardiopulmonary or transient in nature.

In each of the phases of transitional distress characteristic complications occurred. The complications occurring in Phase 3 were atelectasis, hyaline membrane disease, and congestive failure. Eight of the 41 patients had clinical atelectasis during Phase 3. Hyaline membranes were found at autopsy in the lungs of the 2 premature infants who expired during Phase 3. Hyaline membrane disease may perhaps be considered to result from the combination of extrinsic factors (of transitional distress) and the intrafetal factor of an immature lung.[22, 23] Congestive failure was noted at birth in 2 infants and in 4 it developed while the infant was in Phase 3. Congestive failure may be attributed in part to the effects of asphyxia or anoxia on the myocardium.[24, 25]

In Phase 2 seizures, apnea, and intractible vomiting were complicating

disorders. All these evidences of neural hyperexcitability were noted as the rapid regular respiration of the early Phase 2 began to decline. The underlying disturbance of a neuron, resulting from prior hypoxia, may become evident only as oxygenation is improved.[14] With the hyperventilation of early Phase 2 and the resultant alterations in pH and Ca/K ratio, the stage is set for exaggerated neuronal activity. The evidences of neural excitation reported here are probably analogous to the neuromuscular hyperexcitability which has been described by Craig and Buchanan[26] in association with hypocalcemia.

In the small premature infants apnea associated with minimal extensor-flexor movements was observed. This activity may represent an exaggeration of the normal mechanisms regulating breathing as described in apneusis by Hoff and Breckenridge.[27] Vomiting may be due to the neural hyperexcitability, the increased intracranial pressure of the posthypoxemic state,[28] the abdominal distention associated with sympathetic predominance, or the hypersensitive gag reflex frequently seen during this phase. Hyperbilirubinemia (12 mg. per cent or over) occurred during Phases 1 and 2 in six instances in which blood incompatibility was not demonstrable.

Prolonged pulsation of the umbilical artery may be considered to be an abnormal physical sign occurring during the period of transition after delivery. It is postulated that the umbilical vessels may pulsate as the contractility of the vessel wall is diminished or the systemic pressure is increased. The cord may continue to pulsate after delivery if the infant fails to breathe and thus fails to initiate the sequence of events resulting in the cross over of the fetal to the neonatal circulation. The cord may pulsate during Phase 3 and lower Phase 2 when the muscle contractility is poor as a result of inadequate oxygenation. The cord may cease to pulsate when the sympathetic effects of Phase 2 become dominate along with improved oxygenation of the blood or as shock appears at the level of lower Phase 3.

An umbilical artery or vein may bleed during Phase 3 of transitional distress. Arterial hemorrhage associated with cord pulsations has been noted to occur abruptly at the onset of lower Phase 2.

CONCLUSIONS

1. This report describes the clinical behavior of 41 infants whose umbilical arteries continued to pulsate for prolonged periods after delivery.

2. The infants have been divided into groups on the basis of the presence or absence of symptomatology and according to the predominant system involved.

3. Thirty eight of the 41 infants showed evidence of disturbance in transition to extrauterine life. Five expired within 11 hours of birth.

4. The disturbed period of transition appeared to be initiated by (1) disease within the infant (intrinsic or intrafetal disease) or (2) adverse influences in the extrauterine environment (extrinsic or extrafetal disease) or by a combination of the two.

5. Regardless of the major or presenting symptoms of the infants with extrinsic disease, the total symptomatology (transitional distress) followed

a general sequence which could be divided into phases according to cardiopulmonary and neurologic manifestations.

6. Infants with intrinsic disease had symptomatology characteristic of the particular disease present plus symptoms related to superimposed hypoxia. The symptoms of the latter were similar to those seen in extrinsic disease.

7. The maternal histories revealed a high percentage of ante-partum and intrapartum complications (86 per cent). Seventy-three per cent of the infants had either fetal distress prior to delivery or difficulty with the onset of respiration on delivery.

8. It is postulated that transitional distress represents a recovery of the neuraxis subsequent to a prior descending depression which occurred in utero or upon delivery.

9. The respiratory manifestations occurred in three successive phases: Phase 3, labored, Phase 2, rapid, and Phase 1, physiologically labile. The neurologic manifestations likewise occurred in three phases: Phase 3, depression, Phase 2, excitation, and Phase 1, apparent recovery.

10. The complications encountered during Phase 3 were atelectasis, hyaline membrane disease, and congestive failure; during Phase 2, apnea, seizures, and vomiting. Jaundice occurred during both Phase 2 and Phase 1.

11. Prolonged pulsation of the umbilical vessels is one of the physical signs occurring during the phases of transitional distress. It is postulated that umbilical arteries may pulsate after delivery because of a decreased contractility of the musculature brought about by anoxia or asphyxia. Hemorrhage from the umbilical arteries may occur in association with umbilical cord pulsations. The onset of hemorrhage may be abrupt, occurring at the beginning of the phase of neural excitation.

Appendix

Case Reports

Group I. No Observed Disease, Transient Symptomatology Without a Definite Clinical Pattern.—Case 1.—H. R. (Fig. 2), weight 2,410 grams, was born to a 29-year-old multigravida at 40 weeks' gestation. The delivery was complicated by prolonged rupture of the membranes, uterine inertia (stimulated with Pitocin), and breech presentation. Cyclopropane anesthesia was used. At birth the infant was described as limp, pale, and lethargic. She was given endotracheal oxygen under positive pressure because of infrequent gasping respirations. At 30 minutes the infant was pink, had a good cry, and a respiratory rate of 40 per minute. Pulsation of the cord was noted at 1 hour of age. The infant continued to do well and, except for coarse tremors of the extremities between 4 and 6 hours of age, the neonatal period was uneventful.

Group III. Cardiopulmonary Manifestations.—Case 1.—T. E. (Fig. 3) was born to a 31-year-old gravida iv, para i diabetic of 14 years' duration, with a history of two previous stillbirths. A repeat emergency cesarean section under spinal anesthesia was performed at 34 weeks because of hydramnios and slowing of fetal movements. The mother had twice noted a slowing of fetal movement to precede intrauterine death. The amniotic fluid was clear and the fetal heart tones were normal prior to surgery.

The infant cried lustily immediately upon delivery and established apparently normal respiration. The Apgar score was 10 and the cord pulsations were minor. At 3 minutes of age flaring of the alae nasae was noted, and at 7 minutes slight lower sternal

retraction began. At 10 minutes 2 c.c. of amniotic fluid and 15 c.c. of air were removed from the stomach. The infant was placed in oxygen. At 15 minutes the heart rate was 168 per minute. The heart sounds were loud, clear, and regular, with a loud P_2. The cord was erectile and visibly bounding. The infant's color was vivid red in oxygen. The liver was palpable 7 cm. below the right costal margin. At 55 minutes an expiratory grunt became audible and the infant lay inactive, with closed eyes, breathing with great effort. Expiration was longer than inspiration. At 70 minutes the character of physical findings again changed completely while the color remained excellent. Respiration became shallow without retraction or nasal flaring. The heart rate increased; the sounds were still clear and regular; however, the liver size had decreased to 5½ cm. The cry and Moro reflex were normal. In the upper quadrant of the abdomen giant peristaltic waves were noted to travel from left to right. The cord pulsations were again minor in nature.

At 1 hour and 40 minutes of age respiration continued to increase in rate, inspiration was now greater than expiration and it was no longer regular. The heart sounds were as before, but the rate decreased. Peristaltic waves had ceased. At 2 hours the infant began to have spontaneous tremors and hyperactive jerking movements of all extremities. The Moro reflex was found to be repetitive and "pendulum" in type. The hyperactivity increased over a 10 minute period and the infant began to make loud outcries associated with irregular bursts of rapid respiration and tremors of the diaphragm. After 10 minutes of this activity the movements decreased gradually. The cord ceased to pulsate at 2½ hours of age. At 3 hours respiratory rate and heart rate were still increased but the P_2 was not remarkable. The vivid red color had disappeared and the infant showed a slight peripheral cyanosis and circumoral pallor in oxygen. When disturbed by the stethoscope or gavage tube, the infant had the appearance of apprehension and became slightly dusky. At 12 hours of age the infant began to have distention of the left upper quadrant.

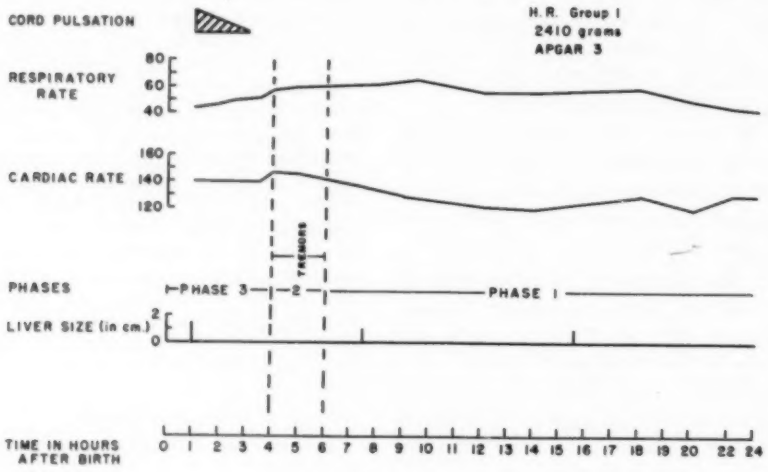

Fig. 2.

The subsequent course was one of gradual improvement. The liver decreased in size to 1½ cm. by 34 hours. For the remainder of the first week of life the infant continued to be irritable when disturbed and had episodes of increased activity along with

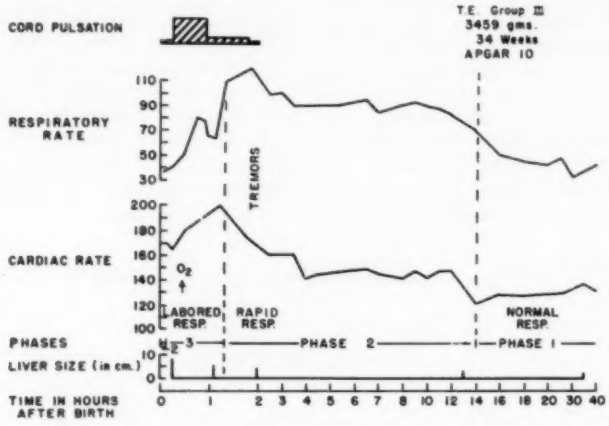

Fig. 3.

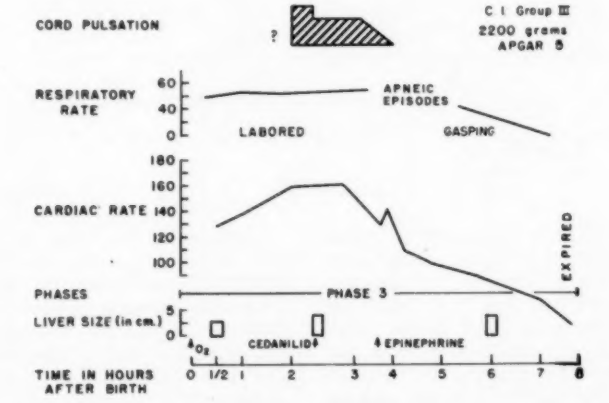

Fig. 4.

many spontaneous startle reactions. The abdomen continued to be slightly distended. Sucking was accompanied by duskiness and therefore the infant was fed by gavage. After 10 days of life the infant had no further difficulties.

Case 2.—C. I. (Fig. 4) was born to a 31-year-old, long-term diabetic of 23 years' duration, with a history of a previous stillbirth and two neonatal deaths. The current pregnancy was uneventful until 33½ weeks when mild hydramnios developed. At 34 weeks the mother noted a decrease in fetal activity and the obstetrician noted a slight irregularity of the fetal heart tones. The infant was delivered by emergency cesarean section under spinal anesthesia because of possible fetal distress. The infant had a weak, spontaneous cry, but the respiratory efforts were poor and the color was cyanotic. An endotracheal catheter was placed in the trachea and oxygen

given by positive pressure. One cubic centimeter of clear amniotic fluid was aspirated from the stomach. Following these procedures, the color improved and the infant was admitted to the nursery and placed in oxygen. At 1 hour of age an expiratory grunt, lower sternal retraction, and an increase in respiratory rate were noted. Peripheral cyanosis and circumoral pallor were present. At 2 hours of age the umbilical cord was noted to be rigid and pulsating vigorously and synchronously with the heart rate. The heart sounds were loud and regular and the P_2 was increased. A systolic murmur, Grade 3, was heard over the left parasternal border. The tinued to appear cyanotic in oxygen. At 4 hours of age the first of a series of apneic attacks began; the color became gray; the general condition gradually deteriorated. The infant expired 8 hours after birth. The postmortem findings were: nonaeration of lungs, petechiae of serous surfaces, dilation of the right heart, early hyaline membrane disease, and pulmonary edema.

This infant had no appreciable tachypnea or tachycardia at any time. She had no period of rapid respiration but went directly from labored respiration to recurrent apnea, with cyanosis, gasping respiration, bradycardia, and death.

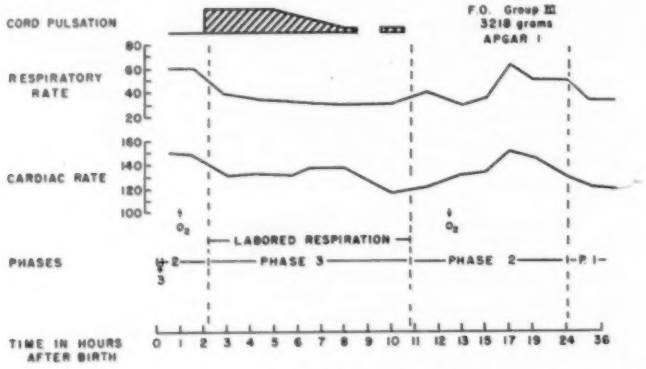

Fig. 5.

forceful heart beat was readily visible over the chest wall. The infant was completely still except for labored respiratory efforts. At 2½ hours the liver was enlarging, and coarse, fine, and wet râles were heard over the lung fields. The heart tones became "mushy" in quality without change in rate. The murmur was no longer heard. Copious mucus was present in the mouth. Rotating tourniquets were applied to the extremities and a catheter was introduced into the umbilical vein for rapid digitalization. Blood rose over the top of the catheter (15 cm.) and was seen to flow simultaneously from both arteries. Heart tones improved briefly, but the infant con-

CASE 3.—F. O. (Fig. 5) was born at term after a normal gestation and a delivery complicated by maternal hypotension during saddle block anesthesia. The infant was atonic, unresponsive, and had a bradycardia (Apgar 1). He responded promptly to endotracheal oxygen and was rated Apgar 9 at 10 minutes of age. At 20 minutes he was breathing quietly but was tremulous. The rectal temperature was 94° F. and the Moro and grasp reflexes were depressed. For 1 hour and 20 minutes after birth the cord did not pulsate. At 2½ hours the infant developed obstructive respiration and visible cord pulsation. Dry crackling râles were heard over

the left base. Air exchange was "fair." Cord pulsations were not palpable between 8 and 9 hours and ceased completely at 10 hours. Labored respirations were absent after 11 hours of age. Physical examination at 24 hours was normal.

tion complicated by ante-partum bleeding and premature onset of labor. Birth weight was 822 grams. Twin "B" was a stillborn.

The infant breathed spontaneously and cried weakly immediately upon delivery. Respiratory distress of the

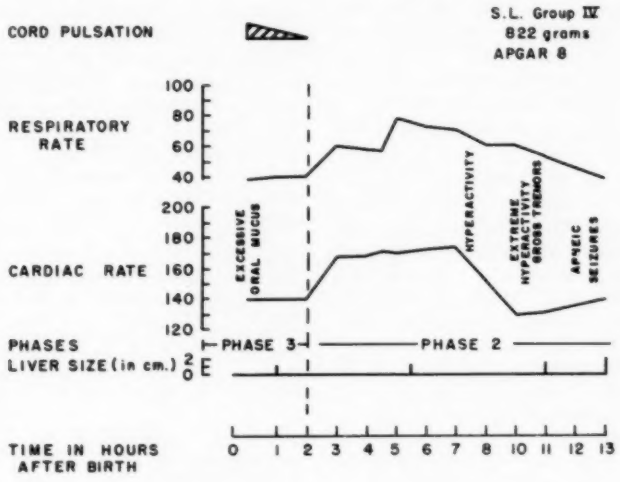

Fig. 6.

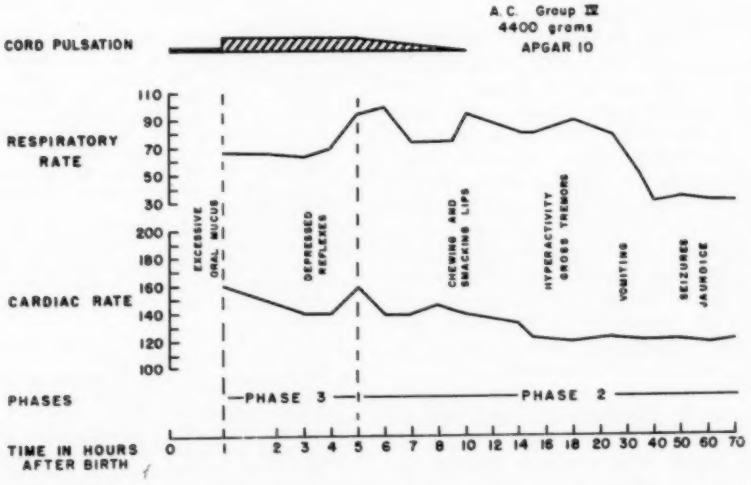

Fig. 7.

Group IV. Neurologic Manifestations.—CASE 1.—S. L., twin "A" (Fig. 6), was born to a 32-year-old multipara after a 32 week twin gesta-

obstructive type began at birth and marked irregularity appeared first at 2 hours of age. At 6 hours hyperactivity, gross tremors, and frequent

jerking movements of the extremities were noted along with irregularities in the heart rate. Excessive activity continued to increase and was followed by episodes of apnea after 12 hours. From 12 hours to the fourth day of life the infant had 3 to 4 episodes daily of pallor and apnea without cyanosis. The infant had frequent spontaneous "startle" movements and was irritable. After 5 days the infant appeared to be progressing well and was discharged from the hospital at 3 months of age at a weight of 2,250 grams.

CASE 2.—A. C. (Fig. 7) weighed 4,400 grams at birth. The infant was born to a 39-year-old, obese, nonregistered multipara with diabetes of short but unknown duration. The infant was delivered at 39 weeks by cesarean section under spinal anesthesia. During the procedure, the maternal blood pressure fell precipitously and was unobtainable for a brief period.

The immediate condition of the infant was good, she cried immediately and respirations were established spontaneously. The infant was edematous and the cord continued to pulsate mildly after delivery.

At 1 hour of age she developed respiratory distress with subcostal retraction and expiratory grunt. Scattered ronchi were heard over both lung fields. The heart rate was 160 per minute, regular, but not loud. Synchronous pulsations were visible over the umbilical cord and palpable over the liver. The infant was placed in oxygen. By 3 hours of age the cyanosis had increased; respiration had become grossly irregular without significant change in rate (66 per minute). Reflexes and response to stimulation were depressed.

At 6 hours of age the infant had a dramatic improvement in color and responsiveness. Respiration became more rapid with minimal sternal retraction. Grunting was absent. Smacking and chewing movement of the lips began at 8 hours, and spontaneous movements and exaggerated response to stimulation at 15 hours. The cry was shrill and vigorous but poorly sustained. At 24 hours after birth the reflexes were obtainable.

At 30 hours frequent vomiting of greenish mucus was noted. Seizure activity began at 48 hours. Respiration was periodic with irregular periods of apnea culminating in cyanosis. Anticonvulsant therapy was begun at this time. From 48 to 96 hours of age the infant had exaggerated reflexes, tremulousness, seizures, vomiting, and hypertonicity. The cry was shrill, sudden in onset, and of short duration.

Improvement began on the fifth day of life. The physical examination was unremarkable at 18 days of life.

We wish to acknowledge with appreciation the assistance of Dr. Clarence A. Brown, Dr. James L. Desmond, Jr., Dr. Clemmie F. Everley, Dr. Donald M. Paton, Dr. James C. Brennan, and Dr. Ralph Druckman, as well as the residents of the Baylor affiliated pediatric and obstetrical programs, and the nurses of the three cooperating nurseries.

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CONGENITAL NEPHROTIC SYNDROME

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THE idiopathic nephrotic syndrome is a disease of childhood, the onset of which usually occurs in children between the ages of 18 months and 5 years.[1, 6] There have been very few reports of onset within the first year of life. For example, in a series of 425 cases collected by Barnett and coworkers,[1] in only one instance did the disease become manifest within the first year of the patient's life.

Since 1947, we have observed the nephrotic syndrome in 18 patients who became ill in the first days or weeks of life. Because of the early age of onset, we consider it justified to call these cases *congenital nephrotic syndrome (CNSY)*.[14] The ratio of CNSY to all cases of nephrotic syndrome encountered by us has been almost 15 per cent during the last few years.

Our intention in this paper is to describe CNSY and report on our own experience and study of the 18 cases we have seen since 1947.

LITERATURE

The first reported occurrence of CNSY in the literature appeared in 1942 from Switzerland.[10] Since then, excluding 8 cases described by us earlier,[14] we have found reports of 18 cases (Table I); in addition, Vernier and associates[27] mentioned, but did not describe in detail, 8 cases in which the disease was manifest before the age of 8 months. As will be seen from the years of publication, increasing attention has been paid to the disease. It is our belief that very few of the cases of CNSY have been reported.

TABLE I. CNSY CASES REPORTED IN LITERATURE

YEAR	AUTHORS	NUMBER OF CASES
1942	Gautier and Miville	1
1950	Lyttle and Goettsch	1
1951	Fanconi et al.	3 (siblings)
1954	Kunstadter et al.	1
1954	Eiben et al.	1
1954	Frischknecht et al.	1
1957	Giles et al.	3 (2 siblings)
1957	Hudson (cited by Giles)	2 (siblings)
1957	Dobbs and France (cited by Giles)	1
1957	Vernier et al.	1
1957	Gruskay and Turano	3 (siblings)
Total		18

It is to be noted that CNSY has occurred in several siblings in 4 families. The nephrotic syndrome of older children has rarely been observed in more than one member of a family and is not generally considered to be a familial disease. For instance, Barnett and colleagues[1] observed nephrosis in only 2 siblings of 3 families. There are more familial cases in the material of Fanconi[6]: 17 children of 7 families, which includes 3 instances of CNSY. Nephrosis has been reported once in identical twins.[23]

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*Lecturer of the Journal of Pediatrics Educational Foundation, Autumn, 1958.

MATERIAL

The 18 CNSY cases* in our series came from 12 families with a total of 49 children (Table II). Hence, more than one third (37 per cent) contracted the disease. Eleven infants of these sibships who were born prematurely died in the newborn period. There are no detailed reports of their disease nor were any autopsies performed. This incidence of prematurity (22 per cent) is about 4 times the ordinary rate of prematurity. It also exceeds the rate of ordinary neonatal mortality. There must have been something peculiar in these prematurely born children who died early, and it is very tempting to correlate the incidence of prematurity and death with the CNSY of the other children in the families. If we include the premature infants in the CNSY group, the total morbidity (= mortality) was 29/49 or 59 per cent.

The child with CNSY was the first born in 4 cases, the second child in 4 cases, the third in 1 case, and the fifth in 3 (Table III). In 2 families in which CNSY was diagnosed in the second child, the first born had died. In the families where the affected child was the third or fifth, at least one of the earlier children had died as a newborn infant. In 3 cases the mother had only one delivery, a CNSY child. This shows that there are no regularities in the appearance of CNSY children in families.

TABLE II. CNSY MATERIAL

FAMILIES	NUMBER OF CHILDREN	CASES OF CNSY	PREMATURE INFANTS WHO DIED SHORTLY AFTER BIRTH	HEALTHY CHILDREN
1	5	1	2	2
2	4	3	0	1
3	7	1	3	3
4	6	1	1	4
5	3	2	0	1
6	5	2	0	3
7	1*	1	0	0
8	5	3	1	1
9	5	1	1	3
10	5	1	2	2
11	1	1	0	0
12	2	1	1	0
Totals	49	18	11	20
Per cent		37	22	41

*Mother was unmarried and her address is unknown.

TABLE III. BIRTH ORDER OF THE FIRST CNSY CHILD IN THE FAMILY

BIRTH ORDER	NUMBER OF OCCURRENCE	EARLIER DEATHS
First born	4	
Second born	4	2
Third born	1	1
Fifth born	3	3
Total of families	12	

GENEALOGY

Genealogic studies of CNSY reported by Giles and colleagues[11] showed intermarriages in preceding generations. This was not so in our families; no consanguinity was found. Moreover, our families came from different parts of the country, some from urban and others from rural areas.

In several of our families the parents of CNSY children had many apparently healthy siblings. An exception was family 2 with 3 CNSY

*Since autumn, 1958, we have seen 2 additional cases from new families.

children: the only apparently healthy child of this family was found to have a malformation of the kidneys (renum et ureter duplex) and both sisters of the mother had died suddenly as newborn infants (Fig. 1).

fourth and fifth months of gestation and nausea during her third pregnancy with a CNSY child. With the exception of 4 babies delivered at term, all of the children were born 2 to 8 weeks prematurely. The birth

TABLE IV. PREGNANCY AND DELIVERY

CASE	YEAR	MOTHER	TIME OF DELIVERY (WEEKS BEFORE TERM)	PLACENTA (GRAMS)	BIRTH WEIGHT (GRAMS)
1	1947	Healthy	3	?	2,100
2	1950	Healthy	3	?	2,650
3	1951	Edema	3	1,500	2,800
4	1951	Healthy	5	1,500	2,500
5	1951	Healthy	3	?	2,480
6	1951	Edema	At term, normal	?	3,280
7	1951	Healthy	At term, normal	?	3,250
8	1956	Healthy	At term, normal	?	2,900
9	1952	Healthy	4	?	1,900
10	1958	Toxemia gravid	4	Very large	2,000
11	1953	Healthy	4	?	2,100
12	1955	Skin eruptions (fourth to fifth month of gestation)	3	1,400	2,700
13	1956	Healthy	2	680	2,210
14	1958	Vomitus	2	560	2,320
15	1954	Healthy	6	Very large	1,950
16	1957	Healthy	4	>1,000	1,850
17	1957	Healthy	At term, normal	>1,000	2,320
18	1957	Healthy	8	760	1,840

CNSY does not appear to be sex-linked. Half of our cases were males and half females, although in one family all of the male children were affected and all of the females were healthy. In another family the reverse was true.

Fanconi and associates[6] and Vernier and co-workers[28] report a high incidence of allergic manifestations in familial nephrosis. In our families there was no history of skin allergy or of asthmatic manifestations.

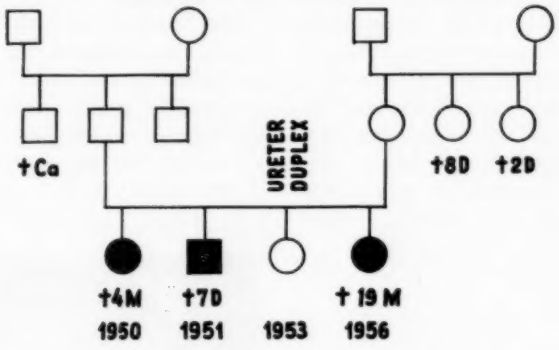
PREGNANCY

The mothers were generally healthy during pregnancy (Table IV). In only one case was it possible to report signs of renal toxemia, pronounced proteinuria, and hypertension. Two other mothers were unusually edematous. One of the mothers had eczema in the

weight was accordingly low. The full-term babies also were relatively light in weight. Assessment of the weight must also take into consideration the edema which appeared in many of the cases soon after birth. In addition, greenish turbidity of the amniotic fluid which was present in most instances must be regarded as a sign of fetal asphyxia. High prematurity rates and a comparatively low birth weight for the gestation time point, in our opinion, to the onset of the disease during the fetal period.

The very large placenta (Table IV) in some of the cases suggests a fetal disturbance. In 10 of our 18 cases for which we have information, the weight of the placenta exceeded the usual weight of 500 grams and it was heavy in comparison to the size of the baby. We were unable, however, to

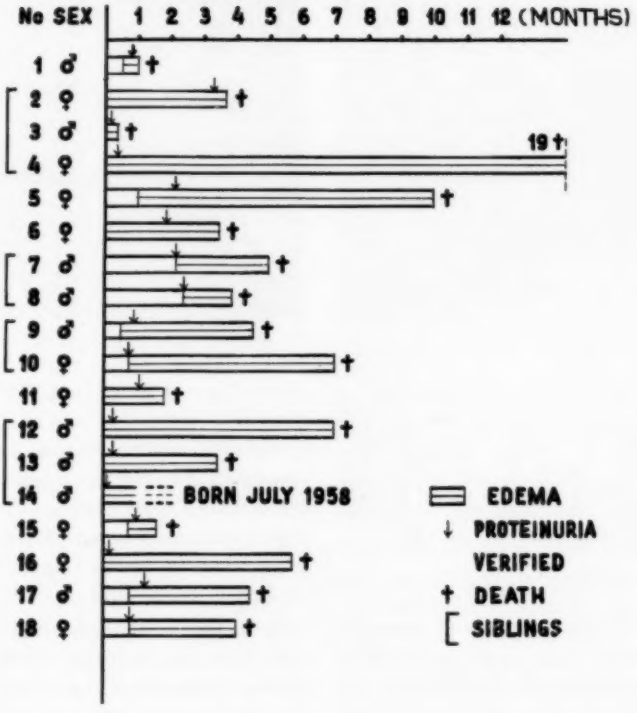
FIG. 1. GENEALOGICAL TABLE OF FAMILY 2



FAMILY: SAIKKONEN (CASES 2,3,4)

Fig. 1.—+ = dead; D = days; M = months; Ca = carcinoma.

FIG. 2. APPEARANCE OF EDEMA AND PROTEINURIA AND COURSE OF CNSY.



obtain a single placenta for examination. It is also impossible to estimate the exact time at which the umbilical cord was cut, a factor which naturally affects the weight of the placenta. Even allowing for these reservations, the majority of the placentas were larger than average.

Although placentas of babies with erythroblastosis are generally large, there was no indication of early icterus in the histories of any of our infants with CNSY. Nothing unusual was found in the blood counts of the infants whose case histories were followed from the first day of life.

Fig. 3.—Edema of a CNSY child 7 days of age.

Fig. 4.—Case 4, child is 18 months of age.

CLINICAL COURSE

Fig. 2 shows the time of onset of the symptoms, proteinuria and edema, as well as the fate of the children. In 8 cases edema was established soon after birth. A typical appearance of the edema some days after birth is seen in Fig. 3.

Fig. 2 shows the time at which the urine was examined for protein and its presence established. The urine was never examined earlier. In some instances the value may have exceeded 1 Gm. per 100 ml. at birth; in others it was clearly lower. Since proteinuria usually precedes the onset of edema by weeks or months,[24] we believe that infants in whom edema was found at about 2 months of age may be described as having congenital proteinuria. Furthermore, the edema was pronounced in all of the patients, suggesting an earlier onset of water retention in the body.

Fourteen of the infants died within the first few months. Only 4 lived beyond 6 months of age (Fig. 2). At the time of this writing, the only one alive is 8 months of age and has all

the symptoms of the nephrotic syndrome. The infants continued to resemble a newborn infant in appearance (Fig. 4). Height and weight development were clearly retarded, the edema notwithstanding. Bone age was low and mental development was fairly slow (Table V).

nephrotic syndrome: high albumin and, compared with serum, low α_2 globulin; gamma globulin was always present.

The protein of the ascites fluid was studied in some instances. The content often was low, varying between 0.1 and 0.8 Gm. per milliliter.

TABLE V. CASE 4: MENTAL AND PHYSICAL DEVELOPMENT OF THE INFANT

AGE (MONTHS)	WEIGHT (GRAMS)	LENGTH (CENTIMETERS)	BONE AGE (MONTHS)	DEVELOPMENTAL AGE ([CATTEL] MONTHS)
Birth	2,500	47		
6	3,760	53		
12	4,100	56	$4 \pm 1\frac{1}{2}$	6-8
18	3,600	56	3 ± 2	9-14

LABORATORY DATA

The symptoms of typical nephrotic syndrome were established in all of the children of our series. As was mentioned, edema was present continuously. Most of the infants suffered from ascites in the initial phase of the disease and several paracenteses were necessary to relieve the condition. The blood pressure measurements and total serum protein levels were constantly low, the lowest value of the latter varying between 1.6 to 3.0 Gm. per 100 ml. of serum.

Serum electrophoresis was obtained repeatedly in most infants by using paper electrophoresis, the method of Antweiler and on some occasions the method of Tiselius. The results were comparable. The albumin concentration was continuously low. The lipoproteins, especially α_2 globulin, were high and the gamma globulin low. The amount of gamma globulin was sometimes almost zero.

Urinary proteins were positive throughout and the content was generally high, although there were fluctuations of the concentration in individual patients. The electrophoretic studies showed typical findings of

Erythrocytes were present in the urine to some extent during the first days of life, disappearing thereafter. In several cases, however, their amount increased as the disease persisted. There were only occasional leukocytes of epithelial cells or casts in the urinary sediment.

Urinary amino acids were determined in 10 cases. The proportion of amino nitrogen in nonprotein nitrogen was clearly below normal. The composition of individual amino acids corresponded roughly to that of normal children.

Urea nitrogen in the blood was low as a general rule, sometimes rising slightly when the disease was of longer duration. No renal clearance tests were performed.

Blood cholesterol was followed consistently. In the initial phase of the disease it may have been lower than 200 mg. per 100 ml. In most cases, however, it was between 200 and 400 mg. per 100 ml. and showed a rising tendency. The highest value determined was 800 mg. per 100 ml.

The antistreptolysin and antistaphylolysin titers were generally low. The mucoproteins and C-reactive proteins determined in a couple of infants

also were commonly low. In one case the former was high (11.2 mg. per 100 ml.) immediately after birth, returning to normal in a few days.

studied. The number of plasma cells was normal in all instances. Furthermore, the auto- and homotransplants performed on the patients surviving

FIG. 5. THE EFFECT OF INTRAVENOUS FAT INFUSION ON BLOOD FAT IN DIFFERENT AGES IN CNSY.

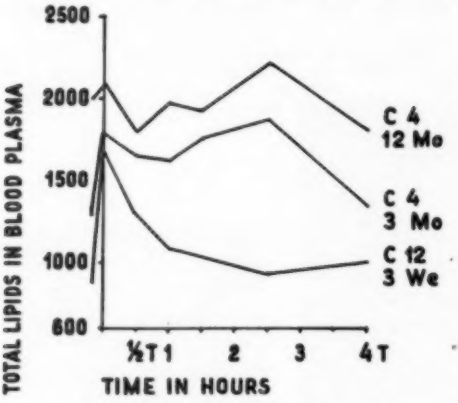


Fig. 5.—C = case; We = weeks; Mo = months.

EXPERIMENTAL STUDIES

Antibodies.—Gamma globulin, as is well known, contains a great part of the antibodies in blood. As was mentioned earlier, the gamma globulin values in our cases tended to be very low. Frequently, they were practically nonexistent from the beginning, as based on electrophoretic determinations. Gamma globulin, however, was constantly found in the urine and in the ascitic fluid.

Gamma globulin levels also were determined serologically in 7 infants, using normal human anti-gamma globulin. In two instances the results were negative and in the remainder it was positive only in dilutions of 1/32 to 1/64.[22, 26] These results correlated with the electrophoretic determinations.

To exclude the possibility of agammaglobulinemia, the bone marrow and biopsies of the lymph nodes were the longest did not resemble the pattern of agammaglobulinemia. The homotransplant was destroyed in the normal manner.

No autoantibodies against the kidneys were found in the serum of 3 infants with the fluorescein technique of Mellors.[20, 21, 26]

Lipid Metabolism.—An intravenous infusion of fat was performed in several infants[17] by administering 2.5 ml. of 20 per cent emulsion per kilogram of body weight (olive oil stabilized with egg lecithin). In healthy infants the fat content returns to normal within 30 to 60 minutes. In patients with the nephrotic syndrome the fat content continues to rise for several hours.

Initially in infants with CNSY (Fig. 5) the blood fat curve was almost the same as that of normal infants. The cholesterol and total fat content of the serum at this age were

fairly low. As the CNSY progressed, the fat curve approached more and more closely the curve seen in the nephrotic syndrome of older children.

POSTMORTEM STUDIES

An autopsy was performed on 16 infants. One infant (Case 16) died at home, one is still alive. The renal lesions of 8 infants in this series have been reported elsewhere.[14, 15]

Macroscopically, the kidneys were large or normal, never small and cirrhotic. The capsule was easily removed, although sometimes adherent. In no instance did the macroscopic appearance resemble that of kidneys of acute hemorrhagic nephritis nor that of the large, mottled kidneys of subacute nephritis.

Microscopically (Table VI), the kidneys consistently revealed fatty degeneration in the tubular epithelium and in some there was fat in the lumens of the tubules. Dilatation of the tubules was seen very easily, and atrophy was more pronounced in the more advanced lesions of the older infants. The interstitial connective tissue was firmer than normal.

The glomeruli of infants dying soon after birth did not reveal changes characteristic of nephrosis. A slight increase in light microscopy in so-called mesangial cells, however, was evident. The most distinct changes were noted in the basal membranes of the glomerular capillaries which appeared to be thick. These changes could not be postmortem ones, since they were also observed in a 1-month-old infant from whom a renal biopsy was taken.

The older the infant, the greater were the changes in the glomeruli. It was possible to see cellular proliferation, depending on the increase of

TABLE VI. MICROSCOPIC FINDINGS IN KIDNEYS OF INFANTS WITH CNSY

CASE NUMBER	AGE	GLOMERULUS				TUBULES				DIAGNOSIS
		BOWMAN'S CAPSULE	HYALINIZATION	PROLIFERATION	BASEMENT MEMBRANE	EPITHELIAL DEGENERATION	ATROPHY	DILATATION	CASTS	
1	27 days	+	−	+	+	+	+	+	+	Membranous glomerulonephritis
2	3 mo. 11 days	+	+	+*	+	+ +	+	+ +	+	Glomerulonephritis
3	7 days	+	−	+*	+	+ +	+	+	+	Membranous glomerulonephritis
4	1 year 6 mo.	+ +	+ +	+	+ +	+	+	+	+	Glomerulonephritis
5	10 mo.	+ +	−	+	+ +	+ +	+	+ +	+	Glomerulonephritis
6	3 mo. 15 days	+ +	+	+	+ +	+ +	+	+	+	Glomerulonephritis
8	3 mo. 22 days	+	−	+	+ +	+	+	+ +	+	Glomerulonephritis
9	4 mo. 12 days	+	−	+	+ +	+ +	+	+	+	Glomerulonephritis
10	14 days	+	+ +	+	+ +	+	+	+	+	Membranous glomerulonephritis
11	1 mo. 16 days	+ +	−	+	+ +	+	+	+	+	Glomerulonephritis
12	7 mo.	+	+	+	+	+	+	+	+	Glomerulonephritis
13	3 mo. 13 days	+	+	+	+ +	+	+	+	+	Glomerulonephritis
14	4 mo. 16 days	+	+	+	+ +	+	+	+	+	Membranous glomerulonephritis
15	1 mo. 18 days	−	−	+	+ +	+	+	+	+	Membranous glomerulonephritis*
17	7 mo. 20 days	+	−	+	+ +	+	+	+	+	Membranous glomerulonephritis
18	4 mo.	+	+	+	+ +	+	+	+	+	Glomerulonephritis

*Biopsy specimen.

endothelial and mesangial cells. In the most advanced cases there were significant changes in the glomeruli. They were avascular and exhibited thickening in the capsule of Bowman. Between the lobes of the capsules were adhesions and sometimes crescent formations. In some capillary tufts necroses could be noted. In better preserved areas the proliferation was marked. The glomerular changes were most nearly like those of chronic proliferative nephritis.

The other organs did not show any particular changes. There was a slight fatty metamorphosis in the liver. In all instances there were signs of pulmonary infections which might have been the cause of death.

ELECTRON MICROSCOPIC STUDIES

A biopsy specimen was examined by electronic microscopy in 3 of the infants (Patients 10, 17, and 4, at the ages of 1, 5, and 18 months, respectively). Detailed observations have been reported elsewhere[25]; the findings were comparable with those of Farquhar and colleagues[7] and Vernier and coworkers[27] in the nephrotic syndrome of older children. The principal alteration consisted of a loss of the characteristic differentiation of epithelial cytoplasm into numerous foot processes which normally insert into the outer aspect of the basement membrane. The normal brush borderlike epithelial cells in the tubuli were absent in many places and the basement membranes were splitting.

MICRODISSECTION OF THE NEPHRON

Dr. Darmady of England performed the microdissections of the nephron in 2 of our cases (Patients 12 and 11, ages 7 and 4 months, respectively). According to his statement, our cases involved an infantile tubule which lacked the tortuosity of the mature tubule. In this respect the observations resembled those of the familial CNSY reported earlier by Giles and associates.[11] Their cases, however, showed, in addition, a so-called swan neck formation which is typical of some renal lesions associated with aminoaciduria. As mentioned previously, the urinary levels of amino acids of the infants in our series were found to be less than normal.

DISCUSSION

The infants with CNSY observed by us all had the symptoms and pathologic changes of the nephrotic syndrome. The principal differences were the early onset, the familial occurrence, the poor response to therapy, and the consistently fatal termination.

The nephrotic syndrome is only rarely familial; however, the prognosis, even in older children, is relatively poor when it is familial.[6, 27] Familial occurrence suggests *an hereditary origin* of the disease. We were unable to find evidence to support this possibility in our series. To our knowledge, there was no intermarrying even in the earlier generations in any of the families. Moreover, the families were from different parts of the country, some from rural districts and some from cities. The CNSY cases of Giles and co-workers[11] might be mentioned in this connection. Among their cases there were marriages between close relatives. The next largest series of CNSY was in Minnesota, where a considerable portion of the population is of Fenno-Scandinavian origin.[27]

Factors pointing to the *onset of CNSY during the fetal period* are the appearance of symptoms in several instances immediately after birth; the

termination of pregnancy in most instances before term and the relatively small size of the infant at birth; the onset of proteinuria several weeks before the appearance of edema[24] which often was established on the first day of life; the finding of a fetal type of nephron by Darmady; and *the large placenta* in the majority of instances. The placenta requires closer study on the possibility that it may shed light on the etiology of CNSY.

Although the changes in *serum proteins* were typical of the nephrotic syndrome of older children, they were considerably more pronounced in CNSY. Total proteins were extremely low; this was especially true of gamma globulin which was sometimes entirely absent in the blood. It is possible that this has a significance for the prognosis of the disease. Sometimes the relatively scanty excretion of proteins in the urine may be explained by the low serum content. The final cause of death, as a general rule, was pulmonary infection.

In not a single case did *the cholesterol level* attain the high values often found in the blood in the nephrotic syndrome. It must be remembered, however, that the cholesterol content of newborn and young infants is lower than that of older children, and values approaching 200 mg. per 100 ml. must be regarded as high. Total lipoids were not determined, but the plasma of one newborn infant was found to be turbid when the sample was taken. The response to the intravenous injection of fat in infants with CNSY was similar to that of older children with the nephrotic syndrome.

Although all of the clinical symptoms and the pathologic changes including those observed by electron microscopy are identical in CNSY and in the nephrotic syndrome of older children, it is naturally possible that CNSY has another etiology. This will probably be proved by further studies. On the other hand, the examination of CNSY may throw light on the etiology of the nephrotic syndrome, still largely veiled in obscurity.

SUMMARY

The clinical course and postmortem findings of 18 infants with the congenital nephrotic syndrome are presented. The infants came from 12 families with a total of 49 children, 37 per cent of whom were affected with CNSY. Eleven other infants in these sibships were born prematurely and died soon after birth.

With three exceptions, the children with congenital nephrosis were born 3 to 5 weeks prematurely. In the cases for which information is available, the placenta was large.

Edema frequently occurred immediately after birth and was present in all of the infants by two months of age, by which time proteinuria was pronounced. Changes in the urine and plasma proteins were typical of the nephrotic syndrome. In the initial phase of the disease no erythrocytes were found in the urine, although some appeared later. The blood urea nitrogen was low, as was the blood pressure.

The plasma cholesterol level was often under 200 mg. per cent, but it rose consistently as the disease progressed. The serum fat curve following intravenous injection of a fat emulsion was also typical of the nephrotic syndrome.

With the exception of one child who is now 8 months of age and still

suffering from the disease, all of the infants have died, the oldest at the age of 19 months.

Postmortem examinations showed the kidneys to have changes typical of the nephrotic syndrome. In the patients who died at the earlier ages the changes in the basement membranes of the glomerular capillaries were mild; more numerous proliferative changes were found in the patients dying later. Fatty degeneration was always present in the cells of the tubules.

The absence of typical foot processes and of splitting of the basement membranes was established by electron microscopy in 3 cases. The tubules had a thickened basement membrane which was lamellar in structure.

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THE BLOOD VOLUME OF INFANTS

I. The Full-Term Infant in the First Year of Life

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THE purpose of this investigation was to observe the changes in total blood, plasma, and erythrocyte volumes and in circulating hemoglobin mass in full-term infants from birth through the first year of life. To this end, serial studies were performed on some of the infants.

The blood volume of infants and children has been examined in several laboratories[1-11] by a variety of techniques. Not all of the results are comparable. There is, indeed, little agreement among the various authors as to the precise constitution of the "true" blood volume and in what manner it should be expressed. It is obvious that, at least in the infant, there should be some common basis of reporting blood volume measurements. None of the methods currently employed are without error or disadvantage; these include dye dilution, Ashby, carbon monoxide, and radioactive tracer techniques and calculation from the plasma or from the erythrocyte volume. Criticism of one method can be met with equally valid criticism of another. We feel that there is the greatest ease of handling, least danger of toxicity, greatest simplicity, and equal reproducibility of results with the use of the azo dye T-1824 (Evans blue). The possibility of hazards from radioactive materials in the young infant limits their use at this time. The erythrocyte differentiation method of Ashby[12] is tedious and, without scrupulous care, subject to sizeable error. The carbon monoxide method requires special equipment and a certain amount of technical virtuosity. Most objections to the dye dilution method have been answered by the work of Gregerson and his colleagues,[13-20] of Barnes, Loutit, and Reeve,[21, 22] and of Mollison and his co-workers.[1, 23, 24] The factors for plasma trapped in the red cell column of the hematocrit tube[23] and for body/venous hematocrit ratio[24] have been used to resolve the difference between blood volumes measured by tagged erythrocytes and plasma. This area of disagreement has virtually disappeared, although it was felt by us that blood volume calculated from the red blood cell volume tends to be too low and that the blood volume calculated from plasma volume tends to be too high. Knowledge of the fate of T-1824 in the circulation and its mixing time in states of health and disease has eliminated many

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Supported by Grant A-515 (C) from the National Institute of Arthritis and Metabolic Diseases of the National Institutes of Health.

doubts as to its accuracy in the measurement of the plasma compartment of the blood.

It is not yet decided whether the measurement of blood volume should be represented on the basis of weight, height, or surface area. In 1929, McIntosh[2] stated, "Since the correlation of blood volume with surface area is not significantly closer than that of blood volume with body weight, there is no material advantage . . . in obtaining the blood volume from surface measurement. . . ." Russell,[3] after comparing values determined on weight, height, and surface area, stated, ". . . up to 13 years of age, weight formed the most reliable basis on which to calculate the blood volume." Karlberg and Lind[4] as a result of their studies with the carbon monoxide method of Sjöstrand[25, 26] agreed with this conclusion. Oliver, Graham, and Wilson[27] have stated, "The customary procedure of using height and weight to calculate the assumed surface of the body . . . is based on confused logic and inadequate observation." It is perhaps not generally realized that the original DuBois[28] formula for deriving surface area from weight and height was based on the study of 10 persons, including an obese elderly female, a deformed child, and an adult dwarf.

It is our conviction that the use of body weight is an adequate means of expression for comparing the blood volume of infants. Differences due to anthropomorphic variations and sex tend to be minimal during infancy. Though some error will be permitted owing to disparity of lean/fat body ratios, these are minor in the first 2 years of life and of rather little importance when one considers the very wide range of values encountered in babies of similar size and proportion.

We are well aware that the measurement of plasma volume is actually a determination of the effectively circulating plasma at the time of sampling and that many factors can influence it, such as altitude, climate, temperature, rest, exercise, disease, and dehydration. Blood volume calculated from the plasma volume, therefore, is the effectively circulating total mass of blood. Possibly, sequestered blood has a physiologic importance in problems beyond the scope of this investigation. There is no doubt that the "true" blood volume is an unknown and incompletely defined entity. More accurate determination can be made with simultaneous measurements of red blood cell and plasma volumes. This technique requires the use of radioactive tracer substances and the withdrawal of such large quantities of blood that it is unsuited to serial studies of infants.

We believe that the volumes derived from measurement of the total circulating plasma, though perhaps higher than those calculated from red blood cell volume, have no greater error.

MATERIALS AND METHODS

The subjects of this investigation were 126 normal full-term infants on whom 223 plasma volume determinations were made. Of these, 2 observations were made on 47 infants, and 3 or more serial observations were made on 20. The infants were born of healthy women attending the obstetric clinic of this medical center,

whose pregnancies and deliveries were uncomplicated. A small majority (60 per cent) of these women exhibited a degree of iron-deficiency anemia at some time during pregnancy, for which most were treated with oral or parenteral iron with varying degrees of success. The subjects of this study are not, then, representative of the entire population but of apparently normal infants attending a pediatric clinic.

No attempt was made to control the environment of the infants. The parity and age of the mothers varied, as did the ancestral histories. Iron deficiency in mothers during pregnancy, a very common condition, is known to have an effect on the red blood cell volume and hemoglobin mass of their newborn infants.[29] Therefore, the values for erythrocyte volume and hemoglobin mass reported in this study may be, to a small extent, lower than those expected in a cross-section of all socioeconomic groups. This does not, however, appear to affect the total blood volume data.

It was difficult to maintain contact with many of the families for the entire period of the investigation; for that reason data are more complete for the early weeks of life than for the latter part of the first year.

Plasma volume determinations were performed with the use of T-1824, after the method of Nitsche and Cohen,[30] using a 0.1 per cent solution in distilled water. A dose of 0.3 mg. per kilogram was administered for each determination. The dye was injected through an antecubital vein or occasionally a scalp vein. Ten minutes after the injection blood samples were drawn from a femoral vein. The injected dye was measured gravimetrically. The dye in plasma was extracted by the method of Allen[31, 32] to avoid the interference of hemolysis or lipemia. The yield was 98±2 per cent.

Hemoglobin concentration was measured by the cyanmethemoglobin method of Crosby, Munn, and Furth[33]; hematocrit was determined by microhematocrit centrifugation; erythrocyte counts were done with standard technique. All determinations were made on a maximum of 3.5 ml. of venous blood at each instance of testing.

Blood volume was calculated from the following formula:

$$\text{Blood volume} = \frac{\text{Plasma volume} \times K}{100 - (\text{Het.} \times 0.95)\ 0.87}$$

$$K = \frac{\text{Concentration standard}}{\text{Concentration sample}}$$

Factor for trapped plasma = 0.95
Factor for body/venous hematocrit ratio = 0.87.

The erythrocyte volume was taken as the difference between the total blood volume and total plasma volume.

The earliest volume measurements were made 10 hours after birth.

RESULTS

A summary of mean values at increasing age periods is given in Table I. A list of values obtained from the serial study of 20 infants is recorded in Table II. It is apparent that there were wide deviations about the means, particularly in the first week of life but notable throughout the year.

Cord blood values were not determined in these subjects since such

TABLE I. SUMMARY OF AVERAGE VALUES: BIRTH THROUGHOUT FIRST YEAR OF LIFE

NO. OF PATIENTS	AGE	WEIGHT (KG.)	HEMOGLOBIN (GM./100 ML.)	HEMATOCRIT (%)	RED BLOOD CELL COUNT (x10⁶)	PLASMA VOLUME (ML./KG.)	BLOOD VOLUME (ML./KG.)	ERYTHROCYTE VOLUME (ML./KG.)	HEMOGLOBIN MASS (GM./KG.)
mean 35	1 day	3.14	17.2	52.3	4.90	55.7	98.2	42.5	17.0
S. D.							±17.4	±9.1	±3.8
S. E. M.							±2.9	±1.5	±0.6
mean 12	2 days	3.18	17.4	53.2	4.92	50.6	90.5	39.9	15.7
S. D.							±8.1	±5.3	±1.9
S. E. M.							±2.3	±1.5	±0.5
mean 28	3 days	3.05	16.8	50.1	4.65	59.8	102.3	42.5	17.2
S. D.							±16.6	±8.4	±3.3
S. E. M.							±3.1	±1.6	±0.6
mean 28	4 days	3.28	15.9	46.8	4.57	60.1	97.8	37.8	15.6
S. D.							±21.2	±9.2	±4.0
S. E. M.							±4.1	±1.8	±0.8
mean 18	5 days	3.48	16.4	49.3	4.77	65.1	110.6	45.6	18.3
S. D.							±20.3	±12.5	±5.5
S. E. M.							±4.9	±3.0	±1.3
mean 5	6 days	3.13	14.8	43.4	4.05	70.6	110.0	39.5	16.2
S. D.							±16.9	±6.1	±2.8
S. E. M.							±7.5	±2.7	±1.3
mean 10	4.0-5.9 (5.4) weeks	4.47	11.6	32.5	3.52	66.6	91.0	24.5	10.5
S. D.							±21.9	±6.9	±2.9
S. E. M.							±6.9	±2.3	±0.9
mean 11	6.0-6.9 (6.2) weeks	4.53	11.1	33.0	3.24	67.9	93.3	25.5	10.3
S. D.							±15.3	±3.9	±1.3
S. E. M.							±4.9	±1.2	±0.4
mean 16	9.0-11.0 (10.1) weeks	5.23	10.3	30.4	3.20	62.5	83.4	20.8	8.6
S. D.							±12.9	±3.0	±1.3
S. E. M.							±3.4	±0.8	±0.3
mean 9	13.0-16.0 (14.6) weeks	5.97	10.5	31.2	3.53	55.0	74.3	19.3	7.9
S. D.							±15.7	±5.6	±2.1
S. E. M.							±5.2	±1.9	±0.7
mean 12	16.0-19.9 (17.8) weeks	6.60	10.6	31.3	3.62	60.0	81.2	21.3	8.6
S. D.							±18.2	±5.8	±2.3
S. E. M.							±5.5	±1.7	±0.7
mean 7	20.0-24.9 (22.5) weeks	6.90	9.8	30.9	4.14	70.7	95.1	24.4	9.3
S. D.							±20.1	±6.3	±2.5
S. E. M.							±7.6	±2.4	±0.9

(Continued on the next page.)

S. D. is standard deviation.
S. E. M. is standard error of the mean.

values bear little relation to the corporeal levels observed a few hours after birth in many infants.

Total Blood Volume.—The values for total blood volume on the first day of life ranged from 69.8 to 137 ml. per kilogram. The mean was 98.2 ml. per kilogram or a total blood volume of 310 ml. By the sixth day, the mean volume had increased to 110 ml. per kilogram, and the range at that time was 89.3 to 140.2 ml. per kilogram. In the fifth week the mean was 91.0 ml. per kilogram, and by the eleventh week it had decreased to 82.1 ml. per kilogram. A further decline to 74.3 ml. per kilogram was observed by the fifteenth week of life. The average blood volume had increased to 95.1 ml. per kilogram by 24 to 25 weeks of age (range 69.5 to 128.5). Another slow decline in the mean volume to 82.9 ml. per kilogram took place by the thirty-sixth week, and the average then remained fairly stable until the fifty-second week when it was 85.6 ml. per kilogram (range 69.0 to 112.2).

We do not believe that the mean volume of 74.3 ml. per kilogram at about 14 weeks of life is necessarily exact. Considering the great variations encountered throughout the year, an average volume closer to those found at 10 and 18 weeks, about 83 ml. per kilogram, might be more precise. Regression lines calculated for these periods are too insecure to settle this point. The more consistent volume increments, both average and individual, between 14 and 25 weeks of life are correct and are compatible with known increases in other peripheral blood values at this time.

Fig. 1 demonstrates the individual values of blood volume of all determinations made. The heavy line represents the means and the shaded

TABLE I—CONT'D

NO. OF PATIENTS	AGE	WEIGHT (KG.)	HEMOGLOBIN (GM./100 ML.)	HEMATOCRIT (%)	RED BLOOD CELL COUNT ($\times 10^6$)	PLASMA VOLUME (ML./KG.)	BLOOD VOLUME (ML./KG.)	ERYTHROCYTE VOLUME (ML./KG.)	HEMOGLOBIN MASS (GM./KG.)
mean 7	25.0-29.9 (26.1) weeks	7.40	10.1	31.4	4.08	65.2	88.2	23.0	8.8
S. D.							±14.5	±5.2	±1.9
S. E. M.							±5.5	±1.9	±0.8
mean 8	30.0-35.9 (33.9) weeks	7.90	9.5	29.8	3.90	62.8	83.2	20.4	7.9
S. D.							±10.1	±3.4	±1.7
S. E. M.							±3.6	±1.2	±0.6
mean 7	36.0-40.0 (37.4) weeks	8.04	10.2	31.6	4.50	60.7	82.1	21.3	8.2
S. D.							±22.9	±5.7	±1.9
S. E. M.							±8.7	±2.2	±0.8
mean 6	50.0-52.0 (51.3) weeks	8.90	9.3	30.1	3.84	66.2	87.9	21.3	8.0
S. D.							±13.3	±2.6	±1.5
S. E. M.							±4.7	±0.9	±0.5

TABLE II. VALUES DETERMINED SERIALLY IN 20 FULL-TERM INFANTS

CASE	AGE	HEMOGLOBIN (GM. %)	HEMATOCRIT (%)	PLASMA VOLUME TOTAL (ML.)	PLASMA VOLUME (ML./KG.)	BLOOD VOLUME TOTAL (ML.)	BLOOD VOLUME (ML./KG.)	ERYTHROCYTE VOLUME TOTAL (ML.)	ERYTHROCYTE VOLUME (ML./KG.)	HEMOGLOBIN MASS TOTAL (GM.)	HEMOGLOBIN MASS (GM./KG.)
1	1 day	9.8	48.0	161	43.5	267	72.1	106	28.6	42	11.4
	10.6 wk.	9.6	32.0	339	59.6	461	81.1	122	21.4	51	9.0
	17.6 wk.	15.8	31.0	485	73.9	652	99.4	167	25.5	64	9.7
	37.6 wk.	11.1	31.0	782	91.8	1051	123.4	269	31.6	101	11.8
2	3 days	16.2	48.5	194	58.6	324	97.7	130	39.2	53	15.8
	9.9 wk.	9.7	30.5	264	45.1	353	60.3	89	15.2	34	5.9
	25.9 wk.	10.6	32.0	631	75.2	858	102.2	227	27.0	91	10.8
	35.9 wk.	9.3	29.0	623	64.9	820	85.4	196	20.4	76	7.9
3	3 days	15.3	46.0	258	76.6	416	123.7	158	47.0	64	18.9
	5.3 wk.	10.7	31.5	387	90.3	523	122.1	136	31.8	56	13.1
	21.3 wk.	10.5	31.0	374	61.3	502	82.4	129	21.1	53	8.7
	25.3 wk.	10.0	32.0	329	51.4	447	69.8	118	18.5	45	7.0
	35.3 wk.	8.8	26.5	397	53.7	509	68.7	111	15.1	45	6.1
4	3 days	15.0	49.0	192	67.0	323	112.7	131	45.6	49	16.9
	10.6 wk.	9.0	26.0	288	75.7	367	96.5	79	20.7	33	8.7
	33.6 wk.	8.8	28.0	412	55.2	530	71.8	124	16.6	47	6.3
5	5 days	21.0	58.0	204	67.5	392	129.8	188	62.2	82	27.3
	10.1 wk.	11.1	30.0	352	71.5	468	95.1	116	23.6	52	10.6
	23.1 wk.	11.6	36.0	488	76.2	695	108.5	207	32.3	81	12.6
6	2 days	17.1	54.0	301	84.2	543	152.1	242	67.8	93	26.1
	10.8 wk.	9.8	26.0	383	57.8	488	73.4	105	15.8	48	7.2
	15.5 wk.	10.8	31.0	294	38.5	395	51.7	101	13.3	43	5.7
7	6.1 wk.	10.8	34.0	235	52.8	326	74.5	92	20.7	35	7.9
	20.7 wk.	9.7	27.5	424	53.7	549	69.5	125	15.8	53	6.7
	28.3 wk.	10.5	30.5	343	37.9	458	50.7	116	12.8	48	5.3
8	2 days	18.8	58.5	164	51.6	318	99.9	154	48.3	60	18.8
	5.4 wk.	12.9	38.0	242	53.8	353	78.0	111	24.6	46	10.1
	9.4 wk.	11.8	36.0	259	49.4	369	70.3	110	20.9	44	8.3
9	4 days	12.6	37.0	230	75.7	331	109.0	101	33.3	42	13.8
	22.4 wk.	7.8	27.0	740	99.8	952	128.5	213	28.7	74	10.0
	51.0 wk.	6.5	25.0	721	89.0	909	112.2	188	23.2	59	7.3
10	3 days	17.5	51.0	190	66.5	328	114.9	138	48.5	57	20.1
	6.6 wk.	9.8	28.0	324	73.4	422	95.5	98	22.1	41	9.4
	19.6 wk.	10.8	32.0	315	51.1	430	69.4	113	18.4	46	7.5

11	4 days	18.0	51.0	170	61.9	293	107.0	124	45.1	53	19.3
	10.6 wk.	10.0	29.0	307	58.4	404	76.9	97	18.4	40	7.7
	25.6 wk.	10.6	33.0	623	77.9	857	107.1	234	29.2	91	11.4
12	2 days	17.7	54.0	170	49.5	308	89.4	137	39.9	55	15.8
	6.1 wk.	12.1	33.0	266	53.7	365	73.8	100	21.1	44	8.9
	14.1 wk.	10.8	33.0	347	55.3	477	76.0	130	20.7	52	8.2
	23.1 wk.	10.8	32.5	437	59.3	598	81.0	161	21.8	65	8.8
	35.1 wk.	10.3	33.5	433	56.2	599	77.8	166	21.5	62	8.0
13	5 days	17.4	57.0	209	53.4	396	101.0	187	47.6	69	17.6
	6.4 wk.	11.4	35.0	385	75.5	542	106.3	157	30.7	62	12.1
	37.4 wk.	10.5	34.0	325	33.1	452	46.0	127	12.9	47	4.8
14	6 days	17.0	51.0	222	66.5	384	115.0	162	48.5	65	19.4
	19.7 wk.	11.0	35.0	351	53.5	494	75.3	143	21.8	54	8.3
	36.7 wk.	10.3	32.0	498	56.2	677	76.4	179	20.2	70	7.9
	45.7 wk.	9.3	30.5	726	79.7	970	106.6	245	26.9	90	7.9
15	3 days	13.3	46.0	146	54.4	236	87.8	90	33.4	31	11.7
	16.3 wk.	7.2	23.0	258	48.5	318	59.8	61	11.4	23	4.3
	24.3 wk.	6.9	27.0	398	63.8	512	82.2	114	18.3	35	5.7
	37.3 wk.	9.4	33.0	436	64.3	599	88.4	163	24.1	56	8.3
16	6.0 wk.	11.6	34.0	238	59.2	331	82.3	93	23.1	38	9.6
	18.0 wk.	11.6	30.0	267	43.7	355	58.1	88	14.4	41	6.7
	27.0 wk.	10.3	31.5	498	69.7	673	94.2	175	24.5	69	9.7
	38.0 wk.	11.3	30.0	361	46.3	480	61.6	119	15.3	54	7.0
	50.0 wk.	11.9	35.0	557	64.6	783	90.9	227	26.3	93	10.8
17	4 days	16.0	44.0	156	54.2	245	85.1	89	31.0	39	13.6
	15.0 wk.	10.6	30.0	311	56.7	413	75.4	103	18.7	44	8.0
	25.0 wk.	10.2	32.5	493	70.4	674	96.3	181	25.9	69	9.8
18	4 days	17.3	51.5	244	73.4	424	127.8	181	54.4	73	22.1
	10.4 wk.	10.8	30.0	279	67.2	372	89.3	92	22.1	40	9.6
	22.4 wk.	11.0	35.0	564	80.3	766	113.6	222	32.9	84	12.5
	36.4 wk.	11.0	32.5	484	61.5	661	84.1	178	22.6	73	9.3
19	5.3 wk.	17.6	46.0	219	54.4	353	87.7	134	33.3	62	15.4
	15.3 wk.	10.0	27.0	287	52.0	370	67.0	83	14.9	37	6.7
	35.3 wk.	12.4	35.0	459	57.4	646	80.8	187	23.4	80	10.0
20	6 days	16.2	45.0	169	63.5	269	101.2	100	37.6	44	16.4
	6.1 wk.	10.3	33.0	344	89.9	472	123.6	129	33.7	49	12.6
	18.1 wk.	10.2	21.0	311	52.9	418	71.1	107	18.2	43	7.2
	38.1 wk.	9.0	29.0	605	72.0	795	94.7	191	22.7	72	8.5
	51.1 wk.	9.3	30.5	478	58.7	639	78.5	161	19.8	59	7.3

area indicates the 95 per cent confidence intervals for each period. Since so many values lie outside of these limits, little reliance can be placed on an average value. The data in Table II confirm this observation in regard to infants studied repeatedly. We have interpreted this to mean that great variability in blood volume exists in these infants both collectively and individually. It would require a far more sophisticated statistical approach to give a refined analysis of the data.

The rather low mean value found at 14 weeks of age could be the result of chance. The four serial observations at this point indicate that a general decrease does occur. Should this not be the case in a larger series, it is unlikely that the mean volume would exceed the values observed before and after this time interval.

The reason for such generally dissimilar total blood volumes during the first year of life is obscure. The relation of bone marrow activity, the influence of iron depletion, and, of course, the natural variability of the individual human are probable concurrent factors.

Fig. 2 illustrates the wide scatter of values when hemoglobin concentration is plotted against blood volume. The most cursory examination of this figure reveals the almost complete lack of relationship between the values. A similar scatter was observed when hematocrit and blood volume were plotted, and a correlation coefficient of 0.26 was calculated, indicating that the blood volume is not dependent on the venous hematocrit.

The total blood volume of the 20 subjects studied at 3 or more intervals was found to increase with the increasing size of the infants in 79 per cent of the 53 observations recorded (Fig. 3), but the increments were not directly proportional, especially before 20 weeks of age. After that time, more parallel increments were noted. This feature is due in part to the differing ratio of vascular area to tissue supplied as growth proceeds.

It can be seen that the assumption of a "normal" blood volume for any infant during the first year is illogical. In addition to the remarkable group variability, blood volume does not remain at nearly as stable a level individually from month to month as it does in the adult.

Plasma Volume.—Considerable divergence from the means was encountered not only in the neonatal period when such variability might be expected but throughout the first year of life. Values established in those infants studied serially also changed extensively at different months of age.

Direct volume determination was the measurement with the least error in computation. It has been confirmed[17, 20] that sampling 10 minutes after injection of dye, as done in this study, is the time at which most thorough mixing in the circulation and the most nearly negligible dye loss are encountered.

There was an increase in the mean plasma volume from 55.7 ml. per kilogram at 1 day of age to 70.6 ml. per kilogram on the sixth day of life. Similar increments were reported by Fashena and her colleagues[5] in their studies of 41 newborn infants. At 4 to 5 weeks of age the mean volume

HGB. CONC. GM./100 ML.

was 66.9 ml. per kilogram. A decrease to 55 ml. per kilogram occurred by the sixteenth week, and a level of 70.7 ml. per kilogram was reached by the twenty-fifth week. A gradual decline to 65.0 ml. per kilogram took place by the fifty-second week.

When the hemoglobin concentration was plotted against the plasma

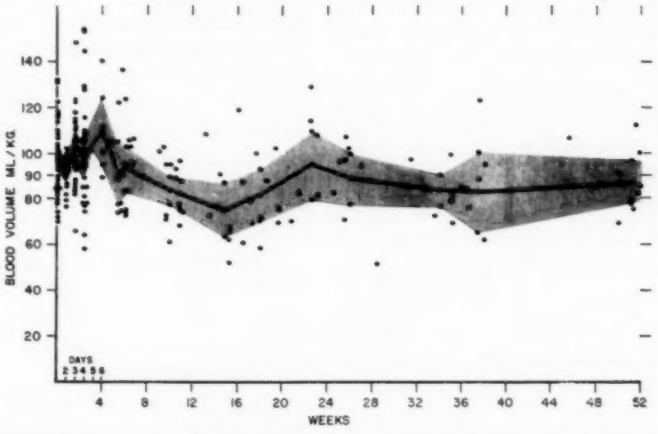

Fig. 1.—Individual values of total blood volume based on kilograms of body weight are plotted against age. The heavy line denotes the means from birth through the first 52 weeks of life. The shaded area represents the 95 per cent confidence interval for each period. Individual values are represented by dots. Many points lie beyond the confidence limits, and it is apparent that the average values are unreliable, particularly in the newborn period.

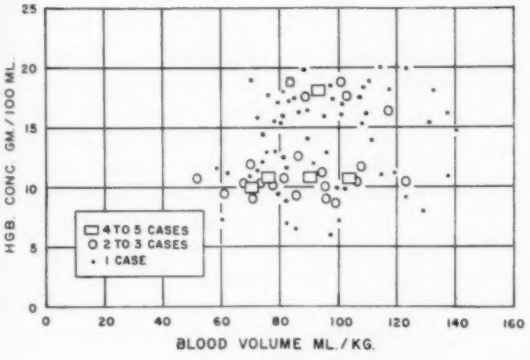

Fig. 2.

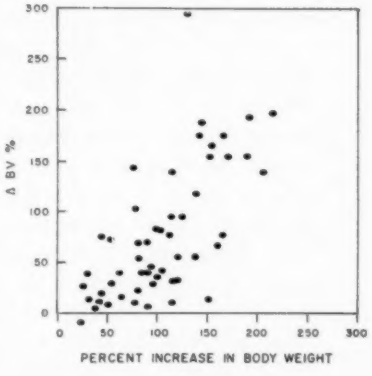

Fig. 3.

Fig. 2.—The wide scatter of values illustrates the lack of relationship of hemoglobin concentration and of blood volume throughout the first year of life. This situation would be duplicated by a graph of hematocrit and blood volume determinations. Since, in this series of infants, the blood volume did not appear to be dependent upon the venous hematocrit, no distinct correlation between blood volume and hemoglobin concentration was expected. The coefficient of correlation was 0.27. Squares represent 4 or 5 and circles 2 or 3 points too closely grouped to reproduce without blurring.

Fig. 3.—The total blood volumes tended to increase as weight was gained, though these increases were not uniformly consistent with size. Greater increments of body weight were noted after 20 weeks of age in the babies studied serially.

volume (Fig. 4), no consistent relationship was noted in either the neonatal period or later. A reason for this may be found in the assumption that at most only 80 per cent of the infants studied could be considered isovolemic. The other 20 per cent (at time of sampling) were regarded as hypo- or hypervolemic. To base a diagnosis of anemia on the concentration of hemoglobin in this large group which was not isovolemic would be erroneous, for in hypovolemia the hemoglobin concentration tends to be normal or elevated out of proportion to the actual circulating hemoglobin mass and in hypervolemia the concentration is frequently far lower than the true mass.

Total Erythrocyte Volume.—A fluctuating erythrocyte volume was noted during the first week of life: high on the first day (42.5 ml. per kilogram), slightly lower on the second (39.9 ml. per kilogram), and higher again on the third day (42.5 ml. per kilogram), in company with fluctuations of the total blood volume. There were similar swings for the rest of the first week. Between the fourth and sixth weeks the red blood cell volume had almost halved, the mean value being 24.5 ml. per kilogram. This level was relatively unchanged until the tenth week when it fell to 20.8 ml. per kilogram. A certain stability was maintained until the twenty-third week, at which time an increase to 24.4 ml. per kilogram was observed. A gradual decrease then occurred. The mean volume at the fifty-second week was 21.6 ml. per kilogram.

Fig. 5 illustrates the percentage loss or gain of this volume in those 20 infants studied serially. In the first 4 to 7 weeks, as might be expected, there was a loss in 5 of 6 infants. During the first 16 weeks, volume determinations revealed a decrease of circulating erythrocytes in 15 of 18 tests. Thereafter, increments steadily outnumbered decrements. The erythrocyte volume did not begin to equal or better the values found in the first days of life until about the sixteenth week.

Total Circulating Hemoglobin Mass.—The circulating hemoglobin mass varies with, and in the same direction as, the erythrocyte volume in the first 6 months of life. Thereafter, though this is still usually so, the appearance of iron depletion may cause individual alterations in hemoglobin mass that are wider than those of the red blood cell volume.

The mean value decreased from 17.0 Gm. per kilogram on the first day to 15.7 Gm. per kilogram on the second, and rose on the third day to 17.2 Gm. per kilogram. On the sixth day the average mass was 16.2 Gm. per kilogram. A sharp decline to 10.5 Gm. per kilogram was seen by the fifth week of life; this decline then proceeded more slowly to a level of 7.9 Gm. per kilogram by the fifteenth week. An increase to 9.3 Gm. per kilogram occurred by the twenty-third week, followed by a decrease to 8.0 Gm. per kilogram at the fifty-second week.

Fig. 6 demonstrates the correlation between the hemoglobin concentration and circulating mass. The relationship is poor except within a narrow range. In the neonatal period

a concentration of 17.5 Gm. per 100 ml. was found in babies of similar birth weight whose actual circulating hemoglobin mass ranged from 13.5 to 26.0 mg. per kilogram. In later months values of from 10 to 11 Gm. per 100 ml. concentration were observed in babies whose mass varied from 5.3 to 14.5 Gm. per kilogram. In general, the higher the circulating

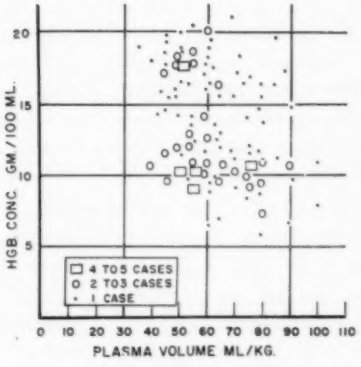

Fig. 4.

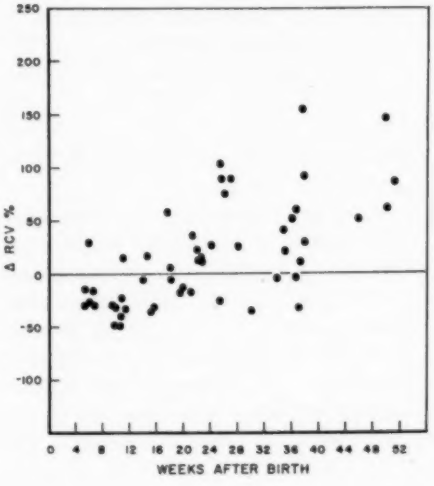

Fig. 5.

Fig. 4.—Points above 15 Gm. per 100 ml. were values obtained during the neonatal period. No consistent relation between plasma volume and hemoglobin concentration could be found in this period or later. Those infants with excessively elevated plasma volumes tended to have low values of hemoglobin concentration, and those with very low plasma volumes tended to have artificially high values of hemoglobin in relation to the age group. Squares represent 4 or 5 and circles 2 or 3 points too closely grouped to reproduce without blurring.

Fig. 5.—The increments of erythrocyte volume from values established in the first week of life did not outnumber decrements until after 16 weeks of age. Poor increments and negative changes after 20 weeks were observed in infants who had or would potentially develop iron-deficiency anemia.

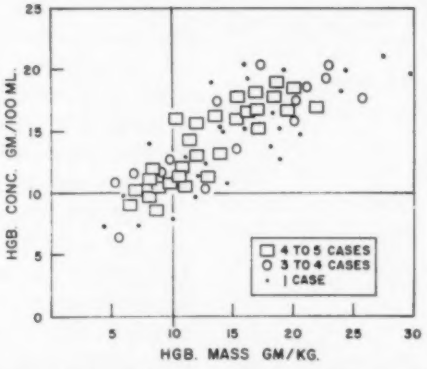

Fig. 6.—Hemoglobin concentration values located above 15 Gm. per 100 ml. on the abscissa were determined in the neonatal period; those below were determined, with few exceptions, between 4 and 52 weeks of age. Squares represent 4 or 5 and circles 3 or 4 points grouped so closely that they could not be reproduced without blurring. Except in a fairly narrow range, correlation between concentration and circulating mass was obscured by conditions of hypo- and hypervolemia. The correlation coefficient was 0.47.

mass, the higher was the concentration. However, for any given concentration the mass was ±4 to 6 Gm. per kilogram or ±⅓ to ½ of the total value per kilogram of body weight.

This is of particular importance in the calculation of iron stores and the projected need for increments of iron later in infancy. The use of cord blood values which are usually lower than postnatal values are probably subject to far greater error.

Fluctuations in the total hemoglobin mass of a few of the infants are difficult to explain. In infants 9 and 20 a drop in the total hemoglobin mass between 7 to 9 and 12 months of age was observed. This may have been due to dietary difficulties of which we were unaware or to abnormalities of iron utilization. The latter is obviously purely speculative.

Infants 11 and 16 demonstrated noteworthy increases of hemoglobin mass in the last interval of study. These infants received diets typical for their ages and developed in an entirely normal fashion. It is apparent from the results recorded that absorption of dietary iron was excellent, the utilization of tissue iron stores was accelerated, and the expansion of the red cell mass was proportionate to growth gain. The responses of these 2 infants to the exigencies of growth was almost ideal.

Hemoglobin Concentration.—Marked variability was found in the first week of life and a slight decline of the average was noted in this period, following a rise on the second day. Narrower deviations from the mean were observed after the fourth week, with relatively stable values decreasing from an average of 11.6 at the fourth week to 9.6 Gm. per 100 ml. at the thirty-fifth week. The mean was 10.1 Gm. per 100 ml. at the fortieth week and 9.3 Gm. per 100 ml. at the fifty-second week. This last value is accounted for in part by the hypervolemia of subject 9. Despite the development of anemia in subjects 3, 4, 7, and 13 between the ages of 9 and 12 months, only rarely was the hemoglobin concentration below 9.0 Gm. per 100 ml. The diagnosis of anemia was actually made only after the erythrocyte volume and hemoglobin mass values were learned, not from the hematocrit or hemoglobin concentration levels.

Hematocrit.—A moderate decrease of the mean value of 52.3 per cent on the first day of life to 48.9 per cent on the fifth day and 43.4 per cent on the sixth was noted. The hematocrit at 4 to 5 weeks of age was 32.5 per cent and at 10 to 11 weeks it was 30.4 per cent. This last value was closely maintained through most of the year.

The hematocrit did not represent the actual circulating erythrocyte volume in most instances, especially beyond the neonatal period. When the hematocrit was plotted against the erythrocyte volume, the coefficient of correlation was 0.46. This demonstrated, in a somewhat crude fashion, a significant lack of relationship between the two values.

Total Hemoglobin Iron.—The average values of total hemoglobin iron, hemoglobin concentration, and circulating hemoglobin mass are illustrated in Fig. 7. The levels of hemoglobin iron were calculated by multiplying the total hemoglobin mass by 3.4 mg., the content of iron in 1 Gm. of hemoglobin.

The mean value recorded on the first day of life was 180 mg. There was a drop to 153 mg. by 10 weeks of age, followed by a gradual increase. The hemoglobin iron had reached the newborn infant's level by 16 weeks. At 25 weeks of age the mean was 224 mg. Except for an insignificant decrease to 213 mg. at 34 weeks of age, there was a slow and sustained rise to 230 mg. by the fifty-second week.

These values are consistent with those reported by Josephs.[34]

It is not our purpose to discuss the partition of body iron in detail. It is necessary to point out, however, that the curve of hemoglobin iron values compared with the curves of hemoglobin concentration and mass indicates an increase of storage iron in the first 8 to 10 weeks of life and a decrease thereafter as circulating hemoglobin iron increased.

The very small gain of hemoglobin iron observed after 26 weeks has led us to assume a depletion of storage iron. The average values recorded in this period were no doubt affected by the pronounced depletion in subjects 3, 4, 7, and 13.

It is apparent that subject 3, despite excellent gain in weight, was unable to recover the value of total hemoglobin mass found at birth. Sometime between 25 and 35 weeks of age, when anemia developed, he drew upon stores of iron to sustain the total hemoglobin mass at a reduced level of 45 Gm. An identical state of affairs seemed to have occurred in subject 4.

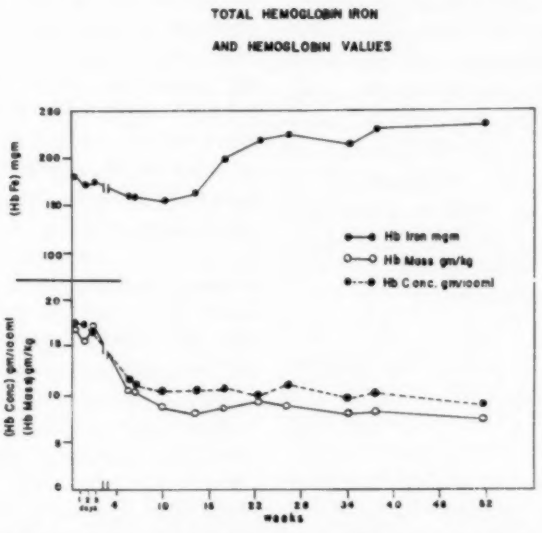

Fig. 7.—The total hemoglobin iron, originally the major iron store of the infant, was at first reduced. A slight increase was observed between the tenth and fifteenth weeks of age. By the sixteenth week its value equaled that at birth. From the eighteenth to twenty-sixth weeks, increments were relatively large but thereafter, except for a slight decrease by 34 weeks, were small. The meager increments after 7 months of age were considered to represent a depletion of storage iron. The only source of iron for the infants, besides the original stores at birth, was from the diet. Medicinal iron was not administered.

Subject 7 was first studied volumetrically at 6 weeks of age. After 20 weeks of age he was unable to increase his hemoglobin mass to keep pace with growth. The erythrocyte volume was low. Since his diet was adequate and his weight gain was normal, it was felt that some difficulty in iron utilization was partly responsible for the low values. The total blood volume was somewhat contracted at the time of each testing. Had it not been for the volumetric studies and for the examination of the blood smears of this infant, the development of anemia would not have been suspected. Unfortunately, contact with this patient was lost after the seventh month.

At 9 months of age subject 13 had developed an iron-deficiency anemia. Owing to hypovolemia, paradoxically elevated levels of hemoglobin concentration and hematocrit were observed. This infant, though clinically healthy and having progressed normally, seemed pale. Anemia was confirmed by examination of his erythrocytes and the low value of hemoglobin mass. At 37 weeks of age the serum iron was found to be 34 μg per cent and the latent iron-binding capacity of the serum was 600 μg per cent, a further confirmation of the diagnosis.

COMMENT

The subjects of this study included 4 infants who developed iron-deficiency anemia. This could not have been predicted upon their selection at birth. The influences producing the anemia could not be evaluated for each individual in the series. The infants studied came from such a mixed background, it is hardly surprising that anemia should have appeared in 4 of them.

The qualifying limits of origin and selection of subjects have weighted the results to some degree. We do not believe, however, that an improper bias was introduced in the combined data. To have selected only those infants of ideal heredity and environment would have given the study an unwarranted and unrealistic distortion. It is illogical to consider an "ideal" group of babies as average or necessarily normal.

We therefore feel that the values of erythrocyte volume and hemoglobin mass and iron presented here are acceptable for infants in the usual urban clinic group and that the blood volume data are representative of most of the general population.

The range of values of the blood volume and its plasma and erythrocyte components is wide from birth throughout the first year of life. This spread is so great that only a profound anemia is apparent in the newborn infant from measurement of the hemoglobin concentration and hematocrit. A 1-day-old infant was studied whose hemoglobin concentration was 19.0 Gm. per 100 ml. The actual circulating hemoglobin mass was only 14.2 Gm. per kilogram. Another infant had a hemoglobin concentration of 14.6 Gm. per 100 ml. but a circulating hemoglobin mass of 21.2 Gm. per kilogram and an expanded blood volume. The infant was plethoric. A diagnosis of anemia in this instance would have been in error.

Since conditions of hypo- and hypervolemia are often not indicated

by the hemoglobin concentration and hematocrit, complete reliance on these laboratory measurements can be misleading. If an estimate of the blood volume is of critical importance in the management of an infant, it should be appraised with regard to other hematologic tests.

It seems clear that the changes in total blood volume during the first few days of life are due less to shifts in the plasma volume alone than to alterations in the quantity of both plasma and erythrocytes. Further study is needed for the correct appraisal of the influence of heat and fluid intake on plasma volume in the early days after birth.

The major iron storage depot in the newborn infant is in the hemoglobin of the erythrocytes. As the infant grows and the vascular bed expands, the iron available for hemoglobin synthesis will come from this original supply and whatever dietary source is accessible. Consequently, a knowledge of the circulating hemoglobin mass is most helpful in the calculation of the degree of anemia or of simple iron depletion. The calculation of erythrocyte volume is also useful, although it is more valuable when compared with the hemoglobin mass. Usually these two values are related.

In this laboratory we have chosen certain values, derived from measurement of the plasma volume, below which we believe an infant 4 to 52 weeks of age is anemic. These are:

hemoglobin mass ------ 8.0 Gm./kg.

red blood cell volume--20.0 ml./kg.

These values are the lowest consistent with adequate synthesis of hemoglobin in the growing infant. They are the points below which we have found a few subjects with a demonstrable anemia.

Reports from this laboratory[35] and Australia[36] indicate that a placental transfusion is not achieved by simple delayed ligation of the umbilical cord, except when the placental blood mass is artificially expressed into the baby. We have therefore felt that the technique of immediate cord ligation practiced at this institution has had no effect on the initial blood volumes recorded here.

The reduction of erythrocyte volume and hemoglobin mass in the first 12 weeks of life was expected. The decrements were mirrored by similar decreases of hemoglobin concentration and hematocrit. Though the diminished values represented a reduction of circulating hemoglobin iron, they did not constitute an actual loss of iron from the body but rather a diversion to tissue. The authors regret that it was impossible to study bone marrow aspirates of the infants. Such study would have given correlative information of erythropoietic activity with the peripheral volumetric changes and also an estimate of iron deposition.

We have concluded that infants, both individually and collectively, up to 1 year of age demonstrate a lack of consistency in the measured plasma, erythrocyte, and total blood volumes. No completely reliable average value was shown during the first year of life, insofar as this might refer to an individual baby. The fact that iron-deficiency anemia can and does occur in the apparently healthy infant by 1 year of age was observed.

SUMMARY

The subjects of this study were 126 normal full-term infants on whom 223 plasma volume determinations were made using a T-1824 dye dilution technique. Of these infants, 2 observations were made on 47, and 3 or more serial observations were made on 20.

Total blood and erythrocyte volumes and total circulating hemoglobin mass values were calculated from the plasma volume, venous hematocrit, and hemoglobin concentration.

No reliable average blood volume could be observed in either the neonatal period or during the succeeding 11 months of life, owing to a wide range of values throughout the year. The average erythrocyte volume, circulating hemoglobin mass, and total hemoglobin iron values did not return to neonatal levels until 16 weeks after birth.

Assessment of anemia in the infant from blood loss, iron deficieney, or other causes can be aided by the determination of the erythrocyte volume and hemoglobin mass. We believe that more reliance can be placed on these values than on those of the hemoglobin concentration and hematocrit because of the considerable number of infants who demonstrate hypo- or hypervolemia. In these states paradoxical values of hemoglobin concentration and hematocrit are frequently encountered which yield misleading information.

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CORRECTED TRANSPOSITION OF THE GREAT VESSELS

Demonstration of a New Phonocardiographic Sign of This Malformation

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SEVERAL important papers have recently been published on the subject of corrected transposition of the great vessels.[1-4] Anderson and coworkers[1] reported that in their series of 21 patients the most frequent associated defects were ventricular septal defects and pulmonary stenosis. Because the unusual anatomy of the coronary circulation, the position of the crista supraventricularis, and the ventricular septal defect in this anomaly present certain technical problems to the surgeon, its preoperative diagnosis is important. Anderson and colleagues[1] were the first to demonstrate the importance of angiocardiography in establishing a diagnosis of corrected transposition of the great vessels. The only clinical case of corrected transposition of the great vessels with a congenital left-sided "mitral" insufficiency without a ventricular septal defect was published by Helmholz and associates.[2] They considered that their patient, a 17-year-old girl, had a "probable" corrected transposition on the basis of findings at catheterization, but they did not demonstrate the abnormal position of the great vessels and the inversion of the ventricles by means of angiocardiography. We, therefore, believe it of interest to report the clinical, phonocardiographic, roentgenologic, electrocardiographic, angiocardiographic, and cardiac catheterization findings in a patient with corrected transposition of the great vessels associated with a probable left-sided "mitral" insufficiency without a demonstrable ventricular septal defect. Also, we wish to describe a previously unreported phonocardiographic sign of this malformation.

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Aided by a grant (H-3518) from the National Heart Institute, United States Public Health Service, and the Chicago Heart Association.

The term "corrected transposition of the great vessels" is used to indicate a natural but anomalous positioning of the great vessels and not a surgically corrected transposition (Ed.).

CASE REPORT

G. McC., an 8-year-old boy, was referred to us on August 17, 1957, because of a heart murmur which had been present since birth. His delivery had been normal and his mother had not been ill during pregnancy. Two other younger children were well and there was no history of rheumatic or congenital heart disease in the family. His physical and mental development were normal, and he played like any normal child. In 1953, he was examined in another cardiac center and a diagnosis of ventricular septal defect was made.

When examined on August 17, he was a well-developed, noncyanotic, white boy who weighed 64½ pounds and whose height was 53½ inches. The blood pressure in the right arm was 110/70 and in the left leg, 120/70 mm.

Hg. The cardiac apex was in the fifth left intercostal space, 1½ cm. to the left of the midclavicular line, and was hyperdynamic and heaving. A systolic thrill was present over the fourth left intercostal space. The first sound was normal, maximal at the apex, and the second sound was loud, maximal at the pulmonary area. A harsh, Grade 4, pansystolic murmur was heard over the fourth left intercostal space and at the apex. This murmur was transmitted with lesser intensity toward the pulmonic and aortic areas and to the left of the apex. A mid-diastolic rumble was present inside the apex.

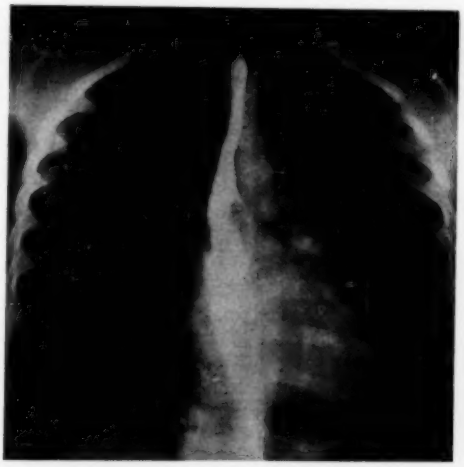
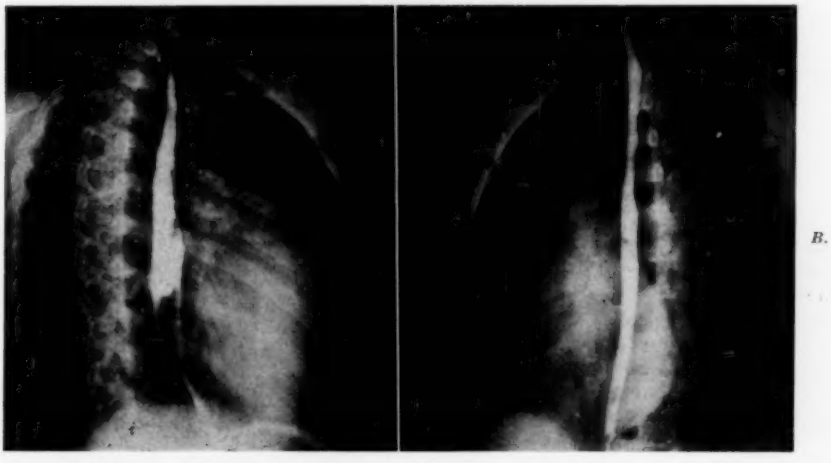


Fig. 1.—P-A view. The pulmonary area is straight and the pulmonary vascular markings are either normal or slightly increased. There is a left aortic arch.



A. *B.*

Fig. 2.—*A*, The right anterior oblique view. There is some posterior displacement of the esophagus in the region of the left atrium. *B*, The left anterior oblique view. The inflow tract of the left ventricle overlies the spine.

Fluoroscopic and roentgenographic examinations in the anteroposterior and right and left anterior oblique views revealed a moderate enlargement of the transverse diameter of the heart. The pulmonary area was straight, and in the left anterior oblique view there was enlargement of the left ventricle. The pulmonary vascular markings and pulsations were considered as questionably increased. A barium esophagram revealed a normal left aortic arch and a slight posterior displacement of the esophagus in the region of the left atrium, suggesting some enlargement of this chamber (Figs. 1 and 2).

The fifteen-lead electrocardiogram revealed a rate of 84 per minute, a P-R interval of 0.22 second, and a QRS of 0.08 second. The limb leads revealed a mean QRS axis of 0 degree and T axis of +30 degrees. The S wave in Lead V_1 measured 28 mm. and the R wave in Lead V_5 measured 30 mm. The tracing also showed abnormally tall and wide P waves and first-degree heart block and was interpreted as consistent with left ventricular hypertrophy and atrial enlargement (Fig. 3). The hemoglobin was 11.6 Gm. per cent. The red blood cell count was 4,180,000 per cubic millimeter, and the white blood cell count, 4,800, with a normal differential count.

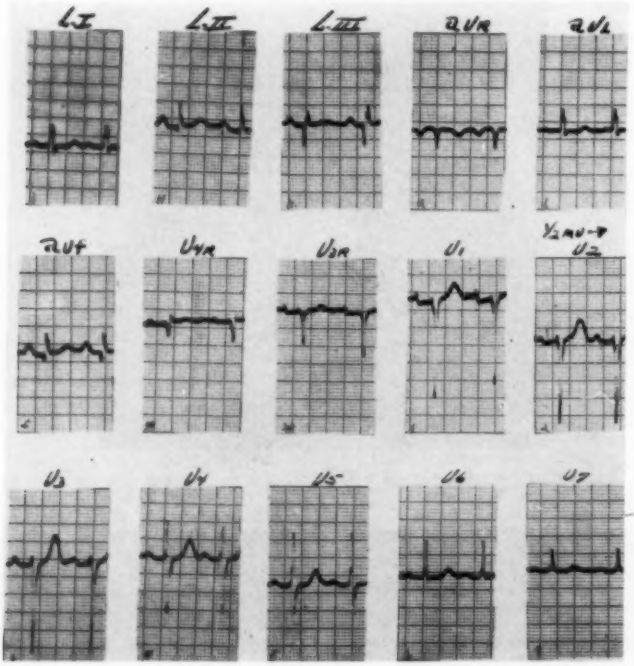


Fig. 3.—The electrocardiogram reveals a first-degree heart block and is consistent with the presence of left atrial and some left ventricular hypertrophy (see text).

Phonocardiograms taken with the stethoscopic and logarithmic methods at a speed of 25 and 75 mm. per second, respectively, confirmed the above-described auscultatory findings (Fig. 4). These auscultatory, roentgen ray, and electrocardiographic findings were, therefore, interpreted by us as

evidences of a ventricular septal defect, and the diagnosis previously made at another cardiac center was accepted.

pass the catheter from the right ventricle into the pulmonary artery (Table I). No evidence of left-to-right shunt was found either at the

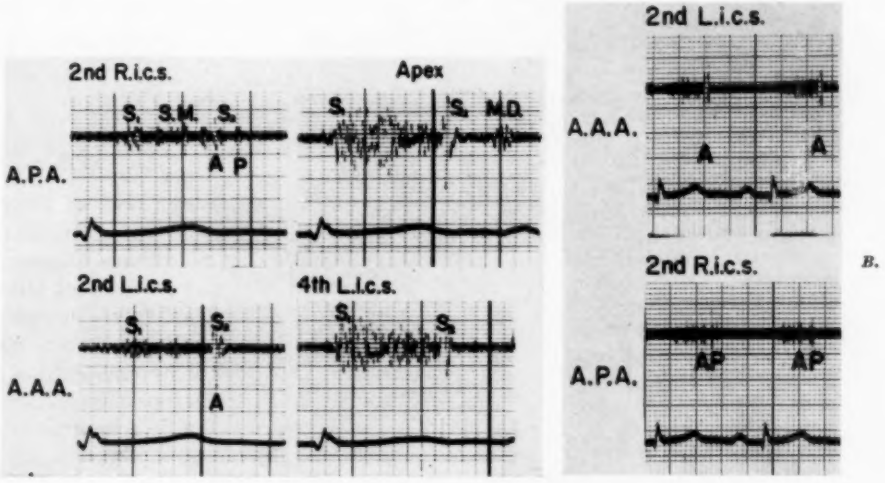


Fig. 4.—*A*, Speed of 75 mm. per second. *B*, Speed of 25 mm. per second. The phonocardiograms reveal a pansystolic murmur, beginning with the first heart sound, maximal at apex and fourth left intercostal space. A mid-diastolic rumble is present at apex. Note the splitting of the second sound over the aortic area.

S_1 = first heart sound.
S_2 = second heart sound.
S.M. = systolic murmur.
M.D. = mid-diastolic murmur.
A = aortic closure.
P = pulmonic closure.
R.i.c.s. = right intercostal space.
L.i.c.s. = left intercostal space.
A.P.A. = anatomic pulmonary area.
A.A.A. = anatomic aortic area.

TABLE I

SITE	OXYGEN CONTENT (VOLUME PER CENT)	HEMOGLOBIN OXYGEN SATURATION	PRESSURE (S/D [M]) (MM. HG)
Superior vena cava	10.91	74	(5)
Right atrium	11.05	75	(5)
Right ventricle	11.33	77	40/4
Femoral artery	14.00	94	80/50 (60)
Hemoglobin oxygen capacity	14.61	—	—

Cardiac catheterization was performed on November 15, 1957, with difficulty due to the occurrence of ventricular tachycardia on numerous occasions when attempts were made to atrial or ventricular levels. An adequate sample was not obtained in the outflow region of the right ventricle immediately proximal to the pulmonary valve, although an adequate

sample was obtained in the right mid-ventricular region. Right ventricular pressure was somewhat elevated. A dye dilution curve (T-1824) with injection into the right atrium disclosed no evidence of a right-to-left shunt. The fact that the catheter could not be advanced into the pulmonary artery[1] and that no evidence of a left-to-right shunt was found, in spite of the auscultatory, radiologic, and electrocardiographic findings of a probable ventricular septal defect, strongly suggested the possibility of our patient having a corrected transposition of the great vessels with a congenital "mitral" left-sided regurgitation without a ventricular septal defect. Angiocardiography was therefore recommended.

Twenty-five cubic centimeters of a 70 per cent Urokon solution was injected into the left cubital vein, and simultaneous anteroposterior and lateral views were taken on the Elema Biplane apparatus as follows: 6 films per second in each view for the first 3 seconds, 2 per second in each view for 2 seconds, and 6 per second in the next 3 seconds. The angiocardiograms clearly revealed the evidence of corrected transposition of the great vessels without a demonstrable ventricular septal defect, and this was based on the following: (1) the contrast substance entering the venous right-sided ventricle which presented the typical configuration of an anatomic left ventricle (Fig. 5); (2) the medial position of the outflow tract of this ventricle and of the main pulmonary artery (Fig. 6); (3) a large left atrium and an ascending aorta originating anteriorly and to the left of the pulmonary artery from an arterial left-sided anatomic right ventricle without reopacification of the right-sided anatomic left ventricle (Fig. 8).* Compare these abnormalities with the angiocardiograms of the normal heart, as shown in Figs. 7 and 9.

*These angiocardiograms were made available through the courtesy of Fay H. Squire, M.D., Chairman, Department of Radiology, Presbyterian-St. Luke's Hospital, Chicago.

DISCUSSION

Since the advent of total cardiopulmonary bypass and the surgical closure of the ventricular septal defect, the preoperative diagnosis of corrected transposition of the great vessels has become a matter of great importance. Anderson, Lillehei, and Lester[1] discussed the physical and laboratory findings in 17 patients, and in the addendum to their paper added 4 additional patients' cases. Most of their patients had associated ventricular septal defects or pulmonary stenosis, and one of them had a persistent left-sided atrioventricular valve stenosis. They stated, "the diagnosis can be definitely established by angiocardiography in the anteroposterior view . . . and the closure of a ventricular cardiotomy is possible, but the unusual pattern of the coronary artery limits the extent of the cardiotomy possible. This poses special problems in surgical exposure." Helmholz, Daugherty, and Edwards[2] are, to our knowledge, the only authors who had previously published a probable clinical case of corrected transposition of the great vessels with left-sided "mitral" insufficiency. Their patient, a 17-year-old girl, did not have angiocardiographic studies. They based their probable diagnosis on the fact that the lateral roentgenogram with the catheter in the pulmonary artery trunk showed the position of the catheter to be considerably more posterior than in normal hearts, on the presence of moderate pulmonary hypertension in the absence of any evidence of a shunt, and on the pulmonary "arterial wedge pressure" being elevated with a contour suggestive of mitral insufficiency.

Fig. 5.

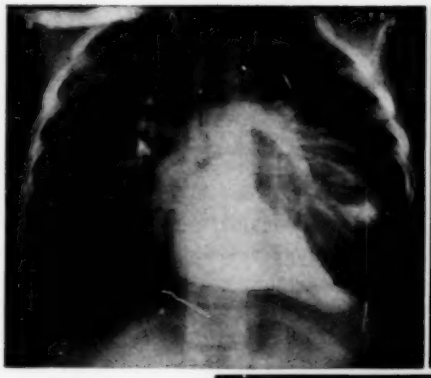


Fig. 6.

Fig. 7.

Fig. 5.—P-A view at 1¼ seconds. The contrast substance enters the venous right-sided ventricle from the right atrium and presents the typical smooth, nontrabeculated appearance of the anatomic left ventricle. Note the prominent "tail" of the ventricle directed toward the cardiac apex.

Fig. 6.—The P-A view at 1⅞ seconds. Note the medial position of the outflow tract of the right-sided venous ventricle and of the pulmonary artery.

Fig. 7.—The P-A view of a normal heart at 1½ seconds. Compare with Figs. 5 and 6.

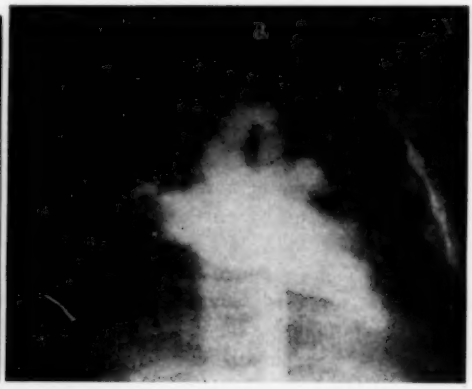


Fig. 8. Fig. 9.

Fig. 8.—The P-A view at 6 seconds. The ascending aorta forms the left upper border of the cardiac outline. The left atrium is enlarged.

Fig. 9.—The P-A view of a normal heart at 6 seconds. Compare the normal configuration with Fig. 8.

Our patient presented physical, phonocardiographic, roentgenologic, electrocardiographic, angiocardiographic, and cardiac catheterization findings that we believe established the diagnosis of corrected transposition of the great vessels with a probable left-sided "mitral" insufficiency without the presence of a demonstrable ventricular septal defect. The systolic thrill, the pansystolic murmur, the hyperdynamic apical impulse, and the loud second sound over the pulmonary area suggested the presence of a ventricular septal defect. The roentgenograms failed to show a medially placed left pulmonary artery, a sign to which we do not attach too much importance since we have seen this in patients with uncomplicated ventricular septal defects and in patients with patent ductus arteriosus. Left ventricular hypertrophy in the electrocardiogram may be present in uncomplicated ventricular septal defects, but first-degree heart block is more commonly present in corrected transposition of the great vessels. Our inability to enter the pulmonary artery led us to suspect that we were dealing with corrected transposition of the great vessels. The angiocardiograms definitely established the diagnosis by demonstrating conclusively that the venous ventricle had the anatomic configuration of the left ventricle, that the main pulmonary artery was medial and posterior, and that the ascending aorta was anterior and formed the left border of the heart. The presence of a pansystolic murmur over the fourth and fifth left intercostal spaces, a mid-diastolic rumble, left ventricular hypertrophy, and the failure to establish the presence of a left-to-right shunt by means of angiocardiography and cardiac catheterization pointed very strongly to an associated left-sided "mitral" insufficiency.

In the light of the angiocardiographic and cardiac catheterization findings we noted an additional, new sign in the phonocardiogram which we had previously missed and which appears to be of importance in the diagnosis of this malformation: The second sound is single at the pulmonary area and is noticeably split at the aortic area. Normally, only the closure of the aortic valve is usually seen at the aortic area. In our patient the aortic area is the anatomic pulmonary area, and this explains the split of the second sound since it represents the normal closure of the aortic and pulmonary valves at the second left intercostal space.[5, 6] Auscultation confirmed the abnormal splitting of the second sound at the aortic area on subsequent re-examination. We failed to find any description or demonstration of this abnormal auscultatory and phonocardiographic sign in any previously reported cases.

Although the corrected transposition of the great vessels in this anomaly may resemble that found in patients with complete transposition of the great vessels, pathologically and physiologically these disorders are quite different (Fig. 10, *A* and *B*). The pulmonary artery in corrected transposition originates from a ventricle which has the anatomic configuration of the normal left ventricle but lies in the usual position of the right ventricle and receives venous blood from the right atrium. The aorta arises from a trabeculated ventricle which presents the muscular landmarks and the crista supraventricularis of the right ventricle but lies in

the usual position of the left ventricle and receives arterial blood from the left atrium. The atrioventricular valves are a mirror image of the normal valves, i.e., the right-sided valve has two leaflets and the left-sided valve resembles the usual tricuspid valve. The relationships of the vena cava, pulmonary veins, and the atria are normal.

logic changes may go unnoticed. Most of these patients, however, have associated ventricular septal defects or pulmonary stenosis, but isolated regurgitation of the left atrioventricular valve is rare. Helmholz and co-workers[2] in their review of 6 autopsied cases found 3 patients who had had a combination of ventricular septal defect and congenital "mitral" insuf-

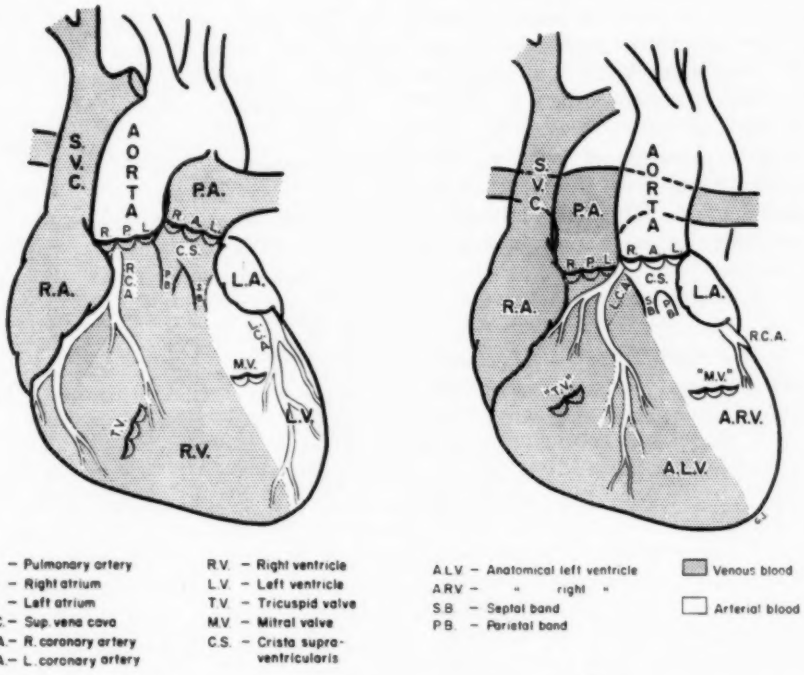


Fig. 10.—*A*, Schematic drawing of the normal heart. *B*, Schematic drawing of the heart in corrected transposition of the great vessels.

There is also usually inversion and transposition of the coronary arteries. If a patient has only a corrected transposition of the great vessels, physiologically the course of his circulation is normal; he may have a normal life expectancy, and it is possible that even at autopsy the above-described pathoficiency. Because cardiac catheterization may fail to identify small shunts and because we were unable to enter the pulmonary artery, a common finding in this anomaly,[1] we cannot, with certainty, exclude the presence of an associated small ventricular septal defect in our patient.

Open cardiotomy and surgical correction of a ventricular septal defect in patients so diagnosed on clinical grounds alone is sometimes advocated. Although we agree that the correlative clinical, roentgenologic, and electrocardiographic findings will establish the diagnosis in the overwhelming majority of patients with ventricular septal defects, our patient presented all the "typical" findings of ventricular septal defect and, had additional studies not been performed, would have been subjected to an unnecessary surgical procedure which is still associated with some mortality. With further progress of surgical techniques, the advisability of surgical correction of the left-sided "mitral" insufficiency on our patient will be reconsidered.

CONCLUSIONS

1. The clinical, phonocardiographic, roentgenologic, electrocardiographic, angiocardiographic, and cardiac catheterization findings in an 8-year-old child with corrected transposition of the great vessels with a probable left-sided "mitral" insufficiency without a demonstrable ventricular septal defect are presented.

2. The splitting of the second sound at the second right intercostal space, which so far as we know has not been previously demonstrated in this malformation, may be of clinical importance in the diagnosis of this anomaly.

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CONGENITAL NEUROCUTANEOUS SYNDROMES IN CHILDHOOD

I. Neurofibromatosis

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CONGENITAL neurocutaneous syndrome refers to a group of developmental anomalies affecting the nervous system, the skin, and occasionally other organs, with marked heredofamilial incidence. The cerebral lesions are clinically evident in epilepsy and mental and motor disabilities. The skin lesions vary from minor pigmentary abnormalities to striking deformity. The recognized entities of the group include (1) neurofibromatosis (Recklinghausen's disease), (2) tuberous sclerosis (Bourneville's disease), and (3) trigeminoencephalo-angiomatosis (Sturge-Weber disease).

These diseases have in common: (1) developmental anomalies involving the brain, the skin, the retina, the skeleton, and the viscera, (2) marked heredofamilial incidence, and (3) frequent coexistence of other types of developmental stigmata.

Whereas these conditions are clear-cut entities both clinically and pathologically, there is at times close resemblance between their various manifestations. A number of patients with one of the diseases may harbor lesions more frequently associated with either of the other two and vice versa. Such pathologically "hybrid forms" will exhibit variant clinical pictures. Definite heredofamilial tendencies have been demonstrated in these diseases, especially in tuberous sclerosis and neurofibromatosis. Cross inheritance may explain the fact that a patient with tuberous sclerosis* was born of a patient with neurofibromatosis.

The literature on this subject has grown extensively in the last fifty years, and a number of terms have been proposed for this syndrome. Yakovlev and Guthrie[1] suggested the name congenital neuroectodermoses, and Van Bogaert,[2] dysplasies neuroectodermiques congenitales. Both of these terms emphasize the ectodermal and neglect the mesodermal aspect of the malformation. Van der Hoeve[3] stressed the heredofamilial *nevoid* factor common to these syndromes and called them phacomatoses. Phacomatoses include, in addition to those disorders already mentioned, hemangioblastoma of the retina and the cerebellum (Lindau-von Hippel disease which does not occur in childhood). Wohlwill[4] believed that the histopathologic changes were indicative of neoplastic malformations and suggested the name hamartoses. However, the term *congenital neurocutaneous syndrome*[4a] seems the most appropriate because it is adequately descriptive and does not exclude mesodermal involvement.

At the Blue Bird Children's Clinic for Neurological Disorders, 6 patients

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*Congenital Neurocutaneous Syndrome in Childhood. II. Tuberous Sclerosis (Case 1), in press.

with neurofibromatosis, 8 patients with tuberous sclerosis, and 9 patients with Sturge-Weber disease have been seen in the past 7 years. Considering the low incidence of these diseases, the number of patients in our series would probably exceed the number seen in most general pediatric practices.

In view of certain difficulties which may be experienced in the diagnosis and management of cases of this kind, an attempt has been made to review the literature and to evaluate these diseases in terms of our own experience. This paper will deal only with neurofibromatosis. The cases of tuberous sclerosis and Sturge-Weber disease will be discussed in subsequent papers.

Von Recklinghausen's neurofibromatosis is a slowly progressive disease which often becomes more apparent with increasing age. In infancy and early childhood the clinical manifestations may be minimal. Café au lait spots on the skin may be present at birth and convulsions may be the only symptom when medical advice is first sought. It is understandable that the diagnosis may be overlooked unless the possibility of neurofibromatosis is kept in mind and the skin lesions searched for with care. The development of mental, speech, and behavior disorders during observation may substantiate the diagnosis.

HISTORICAL

Neurofibromatosis was first described by von Recklinghausen in 1882.[5] The original description concerned only the skin manifestations.*

*Ten years later von Recklinghausen[6] described osteitis fibrosa cystica generalisata, to which his name has also been associated. This is a generalized bone disease due to primary hyperparathyroidism and must not be confused with von Recklinghausen's neurofibromatosis.

Subsequently, it has been shown that neurofibromatosis is a disease of multiple manifestations commonly involving the skin, the brain, the peripheral, cranial, spinal, and sympathetic nerves, infrequently the bony or ocular structures, and occasionally almost every organ of the body.[7]

ETIOLOGY

Neurofibromatosis is a developmental anomaly in which heredity plays an important role. In a study of 115 offspring of 20 patients with multiple neurofibromata, Praiser and Davenport[8] found 43.5 per cent to be affected. Such a high percentage of transmission strongly suggests that the abnormal gene is a mendelian dominant. In the so-called incomplete form of the disease[9] the degree of constancy of a particular clinical form observed in some families also indicates hereditary influence. Thus, members of one family may exhibit neurocutaneous fibromata alone, whereas those of another family may be afflicted with intracranial lesions without skin involvement.

The involvement of tissues of ectodermal (nervous) and mesodermal (connective) origin indicates that the anomalous development commences at an early stage of embryonic life.[10]

PATHOLOGY

Neurofibromatosis is a misdevelopment or dysplasia of the nervous system. It is characterized by diffuse proliferation of the sheaths and enveloping membranes of the nervous system and their supporting structures.[11, 12] Neurilemmoma, progressive fibroma, or neurogenic sarcoma may develop secondarily to neurofibroma.[13]

The individual neurofibroma is composed primarily by hyperplasia of the Schwann sheath cells and fibroblastic proliferation of the supporting structures.[11, 14] It grows in a number of different ways. It may involve the peripheral nerve endings, especially in the skin, and give rise to small noncapsulated nodules with or without pigmentation of the overlying epidermis. The pigment is melanin.[15] Similar lesions may also arise along the trunk of spinal nerves, the median, ulnar, and sciatic nerves being sites of predilection.[16] Of the cranial nerves, the optic, the trigeminal, and the vagus nerves are most often involved in children.[17] Marked thickening and tortuosity of the affected nerves may result and present as disfiguring wormlike masses which are known as plexiform neuromas.[11]

In the central nervous system neurofibroma may develop in the spinal cord and cauda equina and intracranially. Glioma of the optic chiasm is not uncommon in children.[17]

Neurofibroma can affect bone in two different ways: (1) It may develop inside the bone and by pressure produce diffuse rarefaction or cystlike destruction which causes deformities, pathologic fractures, and pseudoarthrosis. (2) Involvement of subperiosteal nerves may induce elephantiac hypertrophy which leads to lengthening and enlargement of long bones and overgrowths of cranial bones.[11, 18, 19]

Outside of the nervous system, massive diffuse hypertrophy of subcutaneous tissues is quite common. When this involves one extremity or a part of it, the condition simulates elephantiasis.[20] Sometimes one or two digits may be bigger than the rest. Such "local gigantism" cannot be explained on the basis of lymphatic obstruction or vascular abnormality. More likely it is a neurotrophic defect. Soft tissue tumors, such as lipoma and diffuse flat hemangioma, have also been reported.[21]

Ocular manifestations are not too common. Congenital glaucoma and neurofibromas involving the lid, iris, cornea, and orbit have been reported.[22] Van der Hoeve[23] noted white platelike tumors in the retina of patients with neurofibromatosis as well as in those with tuberous sclerosis. He coined the term "phacomatoses," signifying "mother spot."

Practically all the viscera may be affected. Neurofibromas of the stomach, intestine, kidneys, larynx, and heart have been described.[24-26] Malignant degeneration is rare and occurs in neurofibromas of deep structures rather than in those of superficial tissues.[27, 28]

The six patients seen in this clinic represent a group which has been selected because of their neurologic disorders, particularly diseases of the central nervous system. Thus, our data are not representative of the average clinical picture in neurofibromatosis.

CLINICAL MANIFESTATIONS

Skin Changes.—

1. *Café au lait spots:* These lesions are flat, discrete, light brown (coffee with milk) in color, and may follow peripheral nerve distribution. These are the most common cutaneous manifestation and occur in all of our six patients (Table I). This pigmentary change is usually present at birth and often more over the trunk. Café au lait spots may appear later or may enlarge with growth spurts of the child. When pigmented lesions stop exactly

TABLE I. CUTANEOUS MANIFESTATIONS IN NEUROFIBROMATOSIS PATIENTS

CASE	PATIENT	SEX/ RACE	AGE FIRST SEEN (YEARS)	AGE LAST SEEN (YEARS)	CUTANEOUS LESIONS		
					CAFÉ AU LAIT SPOTS	SUBCUTANEOUS NODULES	OTHERS
1	W. K.	M/N	2 10/12	5 2/12	Large patches on the arms, trunk, and legs at birth	None	None
2	J. R.	M/W	2 10/12	5 1/12	About 12 on trunk at birth	None	Vitiligo. Mass on left gluteal area
3	J. M.	F/W	15	17 8/12	Small and large patches at birth	Chest, back, arms, and right ear at 11 years of age	Angioma on neck and back
4	C. J.	F/W	8 3/12	12 2/12	Small and large patches at birth	None	Angioma at corner of mouth
5	P. S.	M/M	3 6/12	7 9/12	About 20 over body since birth	None	Plexiform neuroma of left trigeminal since infancy
6	D. F.	M/W	6 1/12	No follow-up	Numerous since birth and more appeared later	None	None

Fig. 1.—Case 1. Negro boy 3½ years of age showing unilateral pigmentation.

at the midline of the body, they are known as true "nevus lateralis.[20] Case 1 in this series presents this picture (Fig. 1).

2. *Subcutaneous nodules:* These lesions usually begin to appear early in life but may develop during adolescence or later. They progress gradually, with new lesions appearing from time to time. They are more numerous over the trunk, fewer over the head, face, and limbs. In our series these lesions were present in Case 3 (Table I).

TABLE II. CLINICAL PICTURE OF NEUROFIBROMATOSIS PATIENTS

CASE	SEX/ RACE	AGE FIRST SEEN (YEARS)	PRESENTING SYMPTOM	NEUROLOGIC EXAMINATION	FAMILY HISTORY
1	M/N	2 10/12	Focal motor seizures	Right side of body larger, supernumerary toes, digits different size	Negative
2	M/W	2 10/12	Generalized seizures	Head large, epicanthal folds, high palate	Negative
3	F/W	15	Psychomotor seizures; convulsive equivalent	Scoliosis	Father has neurofibromatosis, peripheral type, asymptomatic. Brother has subcutaneous nodules in occipital area, asymptomatic
4	F/W	8 3/12	Generalized seizures, about 200, from 6 months to 4½ years of age. Speech defect and poor schoolwork	Right shoulder higher, right hand and foot larger	Negative
5	M/M	3 9/12	Deformity of left face	Plexiform neuroma of left trigeminal nerve	Father has extra thumb. Paternal aunt had two tumors described as "hanging down like grapes" from right ear
6	M/W	6 1/12	Failing vision; headache	Signs of glioma of optic chiasm, with increased intracranial pressure	Mother has many café au lait spots, asymptomatic

A normal person may have a few café au lait spots just as he may have a few nevi. These must not be "overdiagnosed" as manifestations of neurofibromatosis when there are no other demonstrable abnormal findings.

3. *Other skin lesions;* other lesions, such as vitiligo and angiomas, are frequently seen.

While these cutaneous lesions are of diagnostic significance, they seldom give rise to clinical symptoms. In contrast, tumors arising from major nerves and the central nervous system are responsible for most of the symptomatology of the disease. The observations of the skin of our patients are summarized in Table I.

Epilepsy.—Among our patients epilepsy was a common symptom. Four of our 6 patients came with seizures as their chief complaint (Table II). This should not be interpreted as the true incidence of seizures in neurofibromatosis as our patients are a highly selected group and a large proportion of them are referred because of seizures.

The occurrence of seizures is indicative of the presence of primary lesions in the brain. In our small number of patients the seizures were focal or generalized; none had myoclonic or akinetic seizures which were the most prominent seizure types in the tuberous sclerosis group. The seizures tended to occur in cycles and they responded poorly to medication.

Mentality and Behavior.—Depending upon the site and extent of involvement of the central nervous system, varying degrees of mental retardation, speech defect, and behavior disturbance may develop (Table III). In the many cases in which involvement of the nervous system is predominantly in the peripheral nerves, the cerebral functions are largely unaffected even though the appearance of the patient may be distorted by superficial lesions. Case 5 (Table II) with a plexiform neuroma of the left trigeminal nerve was of this kind.

TABLE III. MENTALITY, SPEECH, AND BEHAVIOR IN NEUROFIBROMATOSIS PATIENTS

CASE	AGE (YEARS)	MENTALITY	SPEECH	BEHAVIOR
1	5 7/12	Idiot	None	Hyperactive; unaware of environment
2	5 1/2	Idiot	None	Very hyperactive; unaware of environment
3	15	I. Q. 70 to 75	Normal	Normal
4	12 3/12	I. Q. 70	Defective but understandable	"Nervous"
5	7 9/12	Borderline	Normal	Normal
6	6 4/12	Normal*	Normal	Normal

*Before development of increased intracranial pressure due to glioma of optic chiasm at the age of 4 years.

Other Neurologic Features.—Other specific neurologic symptoms may appear with progression of the disease. In our series Case 1 began to have left focal motor seizures at 9 months of age. Postictal weakness in the left extremities became progressively prolonged until permanent hemiparesis became evident at 2 10/12 years. The gradual increase of symptoms suggests progression of the underlying lesion.

Case 2 developed swelling of the left gluteal region at 4 1/2 years of age. This

swelling was slightly sensitive to touch and lumpy on palpation. Whether this mass was a lipoma or neuroma was not decided as the mother was reluctant to permit biopsy examination.

Case 5 was a Latin American boy with plexiform neuroma of the trigeminal nerve on the left side. He also had associated displacement of the brain, skull defects, and buphthalmos. This case was reported in detail by Podolsky and Fields in 1954.[29]

In Case 5 marked distortion of the cranial and facial bones was caused by a massive plexiform neuroma of the trigeminal nerve.[29] Case 1 was born with 6 toes (2 toes were removed from each foot at 9 months of age so that shoes could be worn), an enlarged right leg and foot, and large second and third fingers (Figs. 2, 3, and 4). Case 2 presented epicanthal folds, a high-arched palate, and macrocephaly. Case 5 was found to have congenital glaucoma at 5 months of age.

Fig. 2.—Case 1. Note congenital enlargement of one leg.

Case 6 developed bilateral proptosis, papilledema, blindness, and other symptoms of marked increase in intracranial pressure due to an advanced glioma of the optic chiasm. The major clinical manifestations are summarized in Table II.

Bone Changes and Other Anomalies.—Bone changes are uncommon in children.[30] Case 3 in our series showed a mild degree of midthoracic scoliosis.

Family History.—In 3 of the 6 patients in this series there was an indication of a familial tendency toward the occurrence of congenital anomalies (Table II). The father of Case 3 had the peripheral type of subcutaneous neurofibromatosis, and this patient's younger brother had subcutaneous nodules in the occipital region, with no detectable clinical symptoms at the time of this writing. The father of

Case 5 had an extra thumb, and a paternal aunt had "dangling" tumors on the right ear. The mother of Case 6 had many café au lait spots on the skin but was asymptomatic at the time of observation.

troencephalogram was abnormal. The findings varied in each case. Case 1 had left focal motor seizures, and his electroencephalogram demonstrated an epileptogenic focus in the right temporal region on two occasions. In the

Fig. 3.—Case 1. Note enlargement of one foot.

Fig. 4.—Case 1. Note enlargement of digits.

LABORATORY FINDINGS

Electroencephalography.—In 4 of our patients who had seizures the electroencephalogram was abnormal. The findings varied in each case. Case 1 had left focal motor seizures, and his electroencephalogram demonstrated an epileptogenic focus in the right temporal region on two occasions. In the other 3 patients slow wave activity or paroxysmal slow activity was found in the tracings. The seizures showed a

gradual change from generalized clonic to tonic or to convulsive equivalent type. Table IV shows the seizure types and the associated electroencephalogram abnormalities.

Roentgenographic Findings.—In every case of suspected neurofibromatosis a bone survey should be made since the bone changes are usually asymptomatic in the early stage. However, bone changes are quite rare in young children.[30]

Pneumoencephalography was done in three of our patients. In Cases 1 and 2 the examination was negative. In Case 5, the patient with the plexiform neuroma of the left trigeminal nerve, a pneumogram at 2½ years of age showed dilatation of the left ventricle. There is also marked enlargement of the left hemicranium and left orbit.

TABLE IV. SEIZURES AND EEG FINDINGS IN NEUROFIBROMATOSIS PATIENTS

CASE	AGE AT ONSET OF SEIZURE OR OTHER SYMPTOM	SEIZURES, TYPE, AND COURSE	EEG FINDINGS
1	9 months	Left focal motor, once every 2 to 3 months; later, limp seizures once every 2 months	13 months: Minimal focal abnormality, right 3 years: Irregular, sharp, slow focal activity, right temporal area
2	8 months	Generalized shaking with cyanosis, 1 to 2 days every 2 to 3 months; later, tonic seizures, same frequency	2 10/12 years: Moderately slow
3	8½ years	Generalized convulsions 1 to 2 per month; later, psychomotor and convulsive equivalents	10 years: Slow for age 15 years: Slow, paroxysmal slow
4	6 months	Generalized convulsions numerous (200), stopped at 4½ years of age	8 3/12 years: Slow dysrhythmia
5	Birth	No seizures; plexiform neuroma of left trigeminal	3½ years: Questionable depression of alpha rhythm and more slow activity in right hemisphere. Sleep: Discharging slow spike focus in left parieto-occipital region
6	4 years	No seizures; glioma of optic chiasm	Not done

DIAGNOSIS

The diagnosis of a fully developed case is usually quite obvious and may be made by inspection alone. In infancy and early childhood when the presenting symptom is a convulsion or mental retardation or speech defect alone, the possibility of neurofibromatosis or tuberous sclerosis should be considered when cutaneous pigmentary lesions are present. A diligent search for cutaneous abnormalities and occult involvement of the skeletal and nervous system may lead to the correct diagnosis.

In performing a biopsy of a suspicious skin lesion total excision is

better than partial excision as the latter may lead to malignant degeneration.[31]

PROGNOSIS

In giving a prognosis to young patients with neurofibromatosis one should be cautious because the course of the disease may be unpredictable. It may remain stationary or develop insidiously. Rapid growth of the neurofibromas or increased pigmentation may occur at puberty or during pregnancy.[32] In itself neurofibromatosis is a benign disease; but the possibility of malignant degeneration or glial proliferation in the brain and spinal cord makes necessary a guarded prognosis. Unfavorable location of seemingly innocuous peripheral nodules, as on the sciatic or ulnar nerves, may prove troublesome. Mental retardation, speech defect, behavior disorders, and protracted epilepsy may gravely affect the life of the patient. Seizures may stop spontaneously, but the other defects usually persist.

TREATMENT

Individual, localized, single, or multiple tumors should be removed only if they cause functional interference. The surgical removal should be as complete as possible because local recurrence is not uncommon even after "complete" excision. Malignant degeneration is another possible complication of incomplete surgery.[31]

X-ray and radium treatment are ineffective.

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". . . the sole cause of the affection was the exposure of the infant to the bright light during the day. . . . This was especially the case among the poorer classes for two principal reasons; 1. Because they live in small rooms, and the bed is consequently near the window. . .; 2. Because many were confined in the lying-in wards of public institutions, where it was usual to have white-washed walls, and large and lofty windows without blinds. . . .

"The worst cases would recover in a week, if only a green blind were placed before the window of the room in which the infant passed the day."

Light the Only Cause of Purulent Ophthalmia of Infants, by T. Ballard. From the British Medical Journal, May 21, 1859.

SPONTANEOUS INTRACEREBRAL BLEEDING IN CHILDREN FROM CRYPTIC VASCULAR HAMARTOMAS

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ALTHOUGH traumatic intracranial bleeding and the accumulation of fluid in the subdural space have become well-recognized entities in pediatric practice, spontaneous intracerebral hemorrhage is not often considered in a differential diagnosis of brain lesions in children. This is especially true when there is no bleeding into the subarachnoid space. The recent surgical treatment of such a case established the fact that a minute vascular anomaly was the underlying cause of the hemorrhage. A review of the literature then made it obvious that while this is not a rare condition it must often go untreated since almost all the pertinent reports are based on autopsy material. These facts prompted the preparation of this paper.

CASE REPORT

C. L., a 10-year-old white girl, hospital number 413467, was admitted to the Strong Memorial Hospital on May 16, 1957. Her chief complaints were lethargy and nuchal rigidity. The child had rheumatic heart disease, with mitral insufficiency and mitral stenosis; she had had acute rheumatic fever at the age of 6 years. There had been no recurrent attacks and no episodes of cardiac decompensation. There had been no recent changes in her heart murmurs. She had been given prophylactic doses of Gantrisin up to the time of her admission. On May 11 her teacher had noticed that she was very listless at school and suddenly fell asleep in class. She was sent home where she remained lethargic. On the following morning at 2 A.M. she awoke and vomited brownish material. She continued to vomit several times a day until her admission to the hospital. That evening and the next day she complained of a headache, became quite confused, and talked in a bizarre fashion. Three days before admission she complained of pain in her neck. She had photophobia and once said that she could not see anything. She remained afebrile, her white blood cell count was 6,000 per cubic millimeter. Shortly before admission marked extensor rigidity was noted in all of her extremities as well as in the trunk and neck.

On examination her temperature was 37.9° C., and the blood pressure was 96/68. The pulse was 68 per minute and regular, and the respirations were 16 per minute. The child was severely ill and uncomfortable. She complained bitterly of posterior neck pain, more marked on the left side. There was no tenderness over the skull, but there was marked nuchal rigidity and tenderness of the neck, most marked on the left side below the foramen magnum. There was a right sixth nerve palsy and a suggestion of a left homonymous hemianopsia. It was difficult to be certain of this because of poor cooperation on the patient's part. The remaining cranial nerves were intact. The deep tendon reflexes were sluggish, but the left

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triceps and ankle jerk were a bit more active than those on the right. There was a Babinski sign on the left. The finger-to-nose test was well done bilaterally, but the heel-to-shin test was performed poorly with the left foot.

The hemoglobin was 14.4 Gm. per cent; the hematocrit was 37; the sedimentation rate, 4 mm.; the white blood cell count was 8,100 per cubic millimeter, with 54 per cent segmented forms, 44 lymphocytes, and 2 monocytes. The platelets appeared to be normal. A roentgenogram of the chest showed the lung fields to be clear, and the cardiac silhouette was somewhat wide to the left and right. Roentgenograms of the skull were not remarkable. A lumbar puncture was performed. The opening pressure was 600 mm. of spinal fluid. The fluid was clear and colorless. Pandy's test was 2+. The fluid contained 20 cells per cubic millimeter. Eleven of these were red blood cells, 5 were polymorphs, and 4 were mononuclears. A Gram stain revealed no organisms. It was thought that the child was suffering from either a viral encephalitis or a tumor.

Within a few hours after her admission she developed a bradycardia, with a pulse rate in the 50's and a bilateral spasticity and loss of positional sense in the lower extremities. A neurosurgical consultation was requested. In view of the signs just described as well as nuchal pain and rigidity, it seemed likely that she had a cerebellar pressure cone. She was taken to the operating room where a ventriculogram was done. The brain was very tense. Only 15 c.c. of air could be injected into the lateral ventricles. Films showed that there was a large mass in the right parietal occipital region. A right parieto-occipital craniotomy was performed. There was no blood over the surface of the brain, but through a transcortical incision in the posterior parietal region a large hematoma was found lying within the posterior portion of the right cerebral hemisphere. It extended forward into the central region. The mass of the hematoma was removed, and several biopsies were made of the wall of the cavity. Grossly, the walls appeared shaggy and brown, stained by blood pigment, but there was no evidence of tumor. Following this procedure, the brain was well decompressed. At the close of the operation the child was alert and answered simple questions accurately. There was marked weakness of the left arm and leg.

The patient made good progress postoperatively, and on the first day after the operation took fluids by mouth. On that day the Babinski signs had disappeared, but there were choreiform movements in the left arm and leg. These were much more marked in the arm. The right sixth nerve palsy remained, and there was a mild ptosis on that side. On May 22, the sutures were removed from the scalp wounds which were well healed.

On the ninth postoperative day she developed a staphylococcal pharyngitis. This was treated successfully with chloramphenicol. However, on June 18 her temperature rose to 38.3° C., and it was discovered that her reticulocyte count was 0. A bone marrow smear was hypercellular and contained numerous megakaryocytes. There was a myeloid hyperplasia, with an increase of promyelocytes and leukoblasts. The hematologist felt that this was an evidence of a dysfunction of red blood cell production due to chloramphenicol. The drug was discontinued at once. On June 28 the reticulocyte count was 2.8 per cent, and subsequently rose to 4.1 per cent. A marrow smear obtained on June 25 was much different from that of June 21. The most striking change was the disappearance of the vacuolization of the early normoblasts.

Neurologically, the child continued to make steady progress and regained the use of her left side. The choreiform movements became much less marked in the upper extremity and disappeared in the lower one. At the time of her discharge there was a slight increase in tone in the upper

Fig. 1.

Fig. 2.

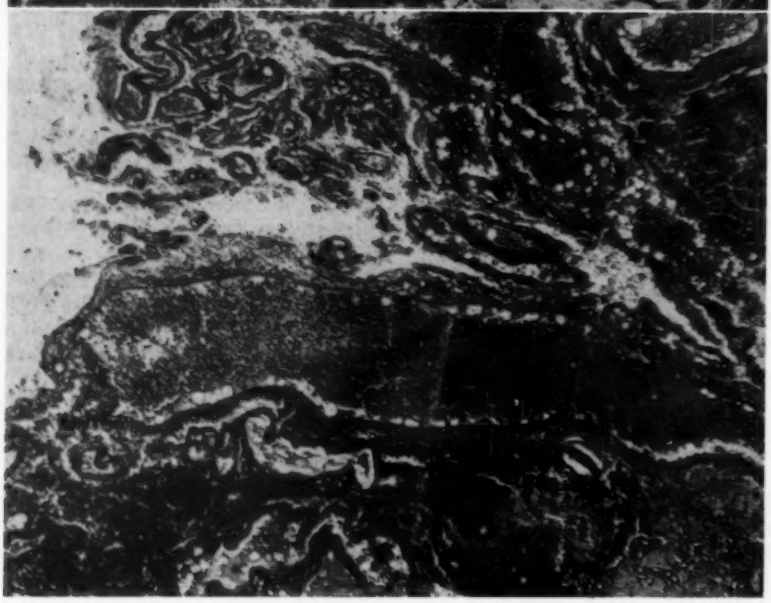

Fig. 1.—Photomicrograph showing the mass of abnormal vessels. Astrocytic proliferation is seen around the vessels (×60).

Fig. 2.—Note the large thin-walled sinusoidal vessel in the midst of the abnormal vessels and the irregularity in the media in other vessels (×60).

extremity. In the left lower extremity there was spasticity of all muscle groups, with hyperextension of the leg and an increase in the deep tendon reflexes. Since that time, the choreiform movements have entirely disappeared as have almost all of the signs of spasticity except for slight muscular rigidity. She plays the piano and runs and plays games without difficulty. There has been no evidence of change in her mental status, and her schoolwork has been unaffected. Her general health has also remained good. The right sixth nerve palsy and ptosis had disappeared by the time she left the hospital.

The biopsies were reported as showing sections of cerebrum with essentially normal architecture except for prominent gliosis in focal areas. In these areas numerous small abnormal vessels were seen. The largest of these were widely dilated sinusoids whose walls were composed of a single layer of endothelium surrounded by a very thin adventitia. Other smaller vessels had a thickened endothelium and in some instances a thickened media as well. These vessels lay both within the parenchyma of the brain and along the pia arehnoid. Between and around them there was glial proliferation (Figs. 1 and 2).

DISCUSSION

In 1922, Hawthorne[1] was struck by the fact that hemorrhages into the parenchyma of the brain, usually fatal in outcome, might occur in otherwise healthy children. Four years later Sheldon[2] reviewed the subject of intracranial hemorrhage in infants and small children. He described both meningeal and brain lesions. In general, he considered the former as traumatic and the latter as complications of nephritis or embolic cardiovascular disease.

Ritchie and Haines[3] discussed spontaneous intracranial hemorrhages in children. One of their patients had an extracerebral aneurysm of the internal carotid artery beneath an optic nerve and presented with visual difficulties. Seven other patients had actually bled intracerebrally, all of whom had bloody spinal fluid. Of this group 3 had large arteriovenous malformations which were seen clearly on arteriography. In 3 no lesion was found. In one child who died shortly after the evacuation of a large clot within the left parietal lobe, microscopic examination of the brain revealed "an angiomatous structure" composed of small malformed vessels.

That such hemorrhages are not rare occurrences in young normotensive adults has long been recognized by neurologists and neurosurgeons. In the past such bleeding was most often ascribed to syphilitic endarteritis, but more recently, as Sprofkin and Blakey[4] have pointed out, a multitude of causes have been found. Both Werner[5] and Daws[6] have recently reported upon small groups of young adults who suffered spontaneous intracerebral hemorrhages. For the most part no etiology was found. In only one of these patients was a small abnormal vein seen on angiography, but it led Daws to suggest that the hemorrhages might have been caused by minute vascular lesions which were too small to be seen on routine angiograms and which had been destroyed by the magnitude of the bleeding itself.

This thought is of interest because in a most thorough review of the various types of intracranial hemorrhage in infancy and childhood, Matson[7] gave the causes as: (1) anoxic conditions associated with delivery, (2) prenatal and obstetrical trauma

to the infant, (3) postnatal craniocerebral injuries, (4) congenital vascular malformations, (5) intracranial tumors, and, in the present instance most interestingly, (6) spontaneous bleeding of entirely unknown etiology. In this final group he placed ". . . those children with spontaneous intracortical bleeding in whom no trauma or vascular disease is present and in whom no source for the bleeding may be disclosed by arteriography, operation, or even routine postmortem examination." He noted that in such cases the hematoma most often lay in the posterior temporoparietal area and that the patient often presented the picture of rapidly increasing intracranial pressure which began suddenly and required an emergency craniotomy. Finally, he thought it probable that the hemorrhages might have been caused by very small, grossly invisible, subcortical vascular malformations, even though he had found none. This was in accord with the opinion of Daws.

Just such small angiomas were described in 6 patients by Margolis and his associates[8] who felt that these lesions were at times the cause of intracerebral hemorrhages. All of their cases were based on autopsy material. Two were found incidentally in young adults dying of other causes while 4 of the patients had died from intracerebral hemorrhages. Interestingly enough, while one of these was 29 years of age, the others were children aged 12, 2½, and 7 years. The youngest child had bled into the pons and was conscious but hemiplegic, with an ipsilateral ptosis. She lived 3 days before dying in coma. The other 2 children both lived 4 days and went from a stuporous to a comatose state, while signs of bilateral pyramidal involvement or decerebrate rigidity developed. In both of them the spinal fluid was clear and colorless. The lumbar puncture pressure was normal in one and not recorded in the other. The clinical picture in these patients is therefore very similar to that of the child described in the present paper. In their cases Margolis and his associates demonstrated either tiny arteriovenous angiomas in the meninges and adjacent cerebral parenchyma or small venous angiomas situated more deeply in the substance of the brain. They pointed out that the four hematomas they described in their patients at post mortem closely resembled spontaneous cerebral hemorrhages of unknown etiology.

In 1956, Crawford and Russell[9] described a group of 20 patients who had bled into their brains from minute vascular abnormalities. The authors called these lesions cryptic arteriovenous or venous hamartomas because they wished to emphasize: (1) the difficulty one has in finding the small malformations at surgery or necropsy, and (2) the fact that these were malformations and not neoplasms. The age of this group is particularly striking: all were under 40 years and 13 were 16 years of age or less. Eight of the 20 had undergone surgery and of these 8, 7 had survived. The remaining 12 had died, and their lesions were discovered at autopsy. The authors described these lesions as small but often big enough to be seen with the naked eye. The lesions were made up of vessels in which the intima and media were abnormal. The muscular and elastic coats might be either thinned out or hyperplastic, and in

the neural tissue between these vessels there were varying amounts of gliosis.

More recently, Bailey and Woodard[10] have described such small vascular malformations of the brain in relation to internal hydrocephalus and mental deficiency as well as in patients dying unexpectedly from brain hemorrhages. The lesions they mentioned were only 5 mm. or so in diameter and, hence, were even smaller than many described by Crawford and Russell. The microscopic descriptions, however, are almost identical and would certainly also fit the lesions described by Margolis as well as that in the child described in this paper. Bailey also stressed the fact that in his opinion such lesions were frequently the source of intracranial bleeding in young people.

On the other hand, 50 intracranial vascular tumors found incidentally at necropsy in patients dying of other causes were reviewed by White and coworkers[11]; only two of them were in infants. They concluded that such lesions were unusual in children. One wonders, however, if those children who had hamartomas which were prone to bleed had not been eliminated by a fatal hemorrhage and thus would be less apt to be included in a group dying of other causes.

In reviewing these reports and the case described in this paper it would appear that there is a specific syndrome of spontaneous intracerebral hemorrhage in children and young adults. Although such bleeding has been described in the past as being of unknown etiology, the probable cause in most instances is hemorrhage from a very small vascular hamartoma.

Usually the child complains of a sudden headache and is drowsy or stuporous. There is no history of significant trauma. Within 2 or 3 hours to a few days the signs and symptoms of a focal cerebral lesion as well as those of progressively increasing intracranial pressure supervene.

On lumbar puncture the spinal fluid pressure may be normal or only slightly elevated. Since the hemorrhage does not often reach the subarachnoid space, the spinal fluid frequently contains no blood, although the number of lymphocytes may be slightly increased.

These findings as well as a mild fever may make a viral encephalitis seem to be the most likely diagnosis at first. However, the lack of systemic signs and symptoms of infection and the presence of progressive neurologic changes should suggest the likelihood of an intracerebral mass for which the only treatment is early neurosurgical removal.

Owing to the marked paucity of reported patients who survived, it is a bit difficult to predict what the future course of these children will be. Matson[7] has stated that the prognosis is quite good because the small angiomas are probably destroyed by the massive hemorrhage. Bailey and Woodard's[10] observation that these hamartomas are usually single would indicate that recurrence is unlikely. It would be valuable if others who encounter such cases and who have pathologic verification of the lesions would report them as well as follow-up studies so that the natural history of the syndrome can be determined.

CONCLUSION

A case of right parietal intracerebral hemorrhage without involvement of the subarachnoid space and without antecedent trauma in a 10-year-old girl is described.

Biopsy of the wall of the hematoma cavity showed the cause of the hemorrhage to be a microscopic vascular hamartoma.

The relationship between such malformations and intracerebral hemorrhage in children is discussed.

The possibility of such hemorrhages should be kept in mind in the differential diagnosis of acute intracranial disorders in children, especially when the signs and symptoms are progressive, because this is a benign lesion which can be cured by surgical evacuation but if left unattended, rapidly causes death.

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SPONTANEOUS RUPTURE OF THE ESOPHAGUS IN A NEWBORN INFANT

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IT is our purpose to call attention to a sudden spontaneous rupture of the esophagus with the secondary development of tension pneumothorax in a newborn infant. Since this condition is rare in the neonatal period and since immediate surgery can be life-saving, a brief note in the literature is felt justified. The term "spontaneous" is used with reservation since the etiology is totally obscure.

Less than 200 case reports of patients with spontaneous rupture of the esophagus have been recorded in the literature. The series reported by Derbes and Mitchell[1] included a 2-month-old child whose death resulted from a pyloric stenosis and in whom an esophageal rupture was demonstrated at autopsy. To our knowledge, this is the youngest patient previously reported.

CASE REPORT

The infant was the sixth child born of a healthy 26-year-old Negro. The mother was seen twice during her prenatal course and the only complication was slight vaginal bleeding 1 month prior to delivery. At 6:17 A.M. on January 14 a 6 pound, 14 ounce female infant was born spontaneously at term. Presentation was vertex, right occiput anterior, and the membranes ruptured just prior to delivery. The infant cried spontaneously and resuscitation was not required at any time.

She was sent to the newborn infant nursery where slight inspiratory retractions were noted by the nurse. At 10:30 A.M. the patient was first examined by a staff physician and again slight retractions were noted. She was placed in humidified oxygen in an incubator and did fairly well until the following day when the retractions became more severe. At the end of 24 hours she was started on routine feedings and tetracycline by mouth. Later in the second day a chest film was made.

Her breathing continued to be shallow and irregular; cyanosis was relieved by administration of oxygen, and she required occasional stimulation with caffeine. Examination revealed decreased breath sounds over the right chest. Penicillin given intramuscularly was added to the therapy during the second night.

The chest film was not seen due to a change in house officers until the following morning, the third day of life. Examination at this time revealed a seriously ill infant with obvious emphysema. She was quite cyanotic and respirations were shallow and rapid. Breath sounds were diminished throughout the right chest. Fine râles were present posteriorly at the left base. The x-ray taken the previous day revealed that the heart and mediastinum were shifted to the left. There was increased radiolucency throughout the right hemithorax and scattered oval and linear densities

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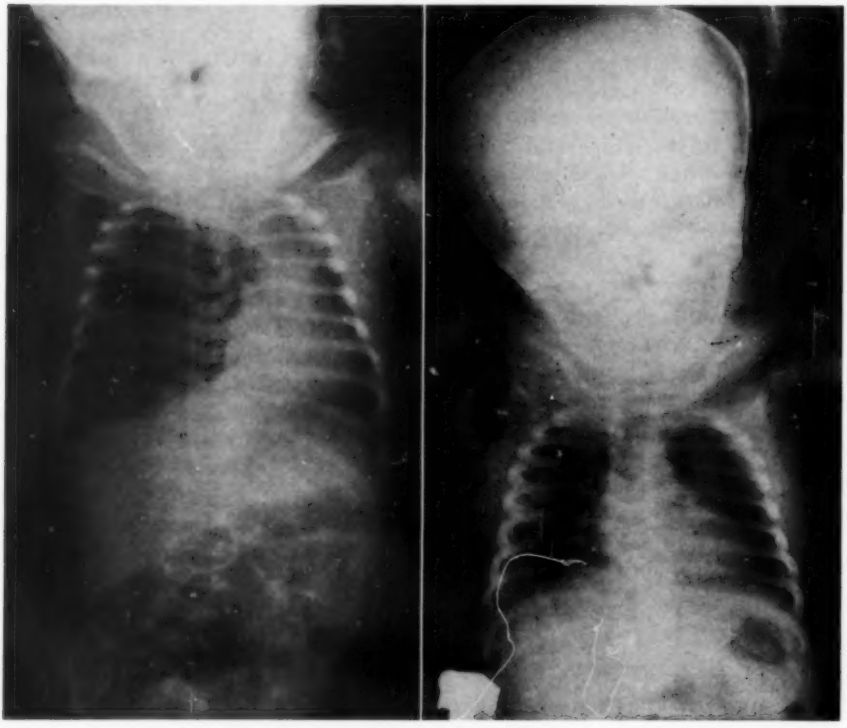
(Fig. 1). It was felt that these findings represented a congenital lobar emphysema or a large cyst. Immediate surgery was felt mandatory.

SURGICAL TREATMENT

A routine right thoracotomy incision was made. Upon opening the chest, a mixture of milk and mucus poured out. After removing approximately 200 c.c. of this material, the atelectatic right lung was identified and rotated anteriorly. A 1 cm. longitudinal perforation with ragged and friable edges was discovered in the midportion of the esophagus on the right side. The patency of the esophagus was demonstrated by passing a polyvinyl catheter into the stomach.

This tube was left in place and the perforation was closed with interrupted sutures of 6-0 silk. The pleura was brought over the closure as a second layer. The chest was closed with three tubes in place, one situated posteriorly near the site of the perforation.

The procedure was well tolerated and the infant was apparently greatly improved.



A. *B.*

Fig. 1.—*A*, Preoperative chest film showing tension pneumothorax on right. *B*, Chest film taken 8 days postoperatively.

POSTOPERATIVE TREATMENT

A chest x-ray on the first postoperative day showed only a slight amount of fluid in the right chest, with complete expansion of the right lung. The thoracotomy tubes were removed on the second postoperative day and an x-ray showed the chest to be clearing at this time.

Penicillin and oxytetracycline were used to combat infection. Glucose water was started by Levin tube on the fourth day and intravenous fluids were discontinued on the fifth day. On the sixth postoperative day an evaporated milk formula was begun by gastric tube, and the tube was removed on the seventh day. Weight gain occurred 12 days postoperatively and on the twenty-first day the infant was discharged to be followed in the clinic. Contrast studies of the esophagus performed before discharge were entirely normal.

The patient has been seen twice in the clinic, the most recent visit being at 2½ months of age, at which time she weighed 9 pounds, 5½ ounces. She was having no difficulties at that time.

DISCUSSION

Considerable attention in the literature has been devoted to spontaneous rupture of the esophagus since the original description by Boerhaave in 1724. Early recognition has become increasingly important since improvements in thoracic surgery have made survival possible. According to Derbes and Mitchell[1] only 35 per cent of the patients survive for 24 hours if surgery is not performed promptly.

The characteristic clinical and roentgenologic features occurring in older children and adults have been adequately described.[1-4] The usual pattern of violent vomiting, followed by intense substernal pain, and associated with subcutaneous or mediastinal emphysema were, of course, absent in this patient. It has been stated that if a pneumothorax or hydropneumothorax develops, subcutaneous emphysema is absent or late in appearance. Tension pneumothorax which has previously been reported in association with rupture of the esophagus[5] was an unusual feature in this patient.

A number of etiologic factors have been suggested.[1, 3, 6] Forceful vomiting and other conditions which could increase intraesophageal pressure such as defecation, epilepsy, etc., have been precipitating factors. In this patient, in whom there was no vomiting, none of these would seem applicable. In a newborn infant intubation or pressure resuscitation would seem to be the most likely cause of a ruptured esophagus. This child, however, breathed spontaneously and was not resuscitated in any fashion. All personnel concerned were diligently questioned immediately following surgery and it is certain that intubation was not performed.

It is highly probable that the catastrophic event occurred at or shortly after delivery since this baby was noted to have some respiratory distress at a few hours of age. It is possible that an esophagus filled with amniotic fluid could be ruptured by sudden extrathoracic pressure such as strong uterine contractions.

Two premature infants recently seen in this hospital were operated on for spontaneous rupture of the stomach. One of these was subsequently autopsied and found to have a congenital defect of the gastric muscularis.[7] Theoretically, such a congenital anomaly could occur in the esophagus. Since this child survived and no sections were obtained, this is sheer speculation.

One further unusual feature in this patient was the location of the perforation. It has been demonstrated experimentally that the weakest section of the esophagus is just above the cardia on the left side. This has been confirmed clinically as the most likely spot for rupture. This lesion occurred on the right side in the middle third

of the esophagus. Subsequent contrast studies have demonstrated no stricture or other abnormality in this area.

Immediate surgery with closure of the defect is the obvious treatment. Early recognition is mandatory. Since our diagnosis was delayed, it is felt that calling attention to this possibility in a newborn infant may alert others to earlier diagnosis. The importance of early roentgenographic examination in any newborn infant with unexplained respiratory distress should be emphasized.

SUMMARY

Idiopathic rupture of the esophagus with a tension pneumothorax in a newborn infant is reported. Immediate surgery with closure of the defect is the only possible therapy. Possible etiologic factors are briefly commented upon.

We wish to express our appreciation to Dr. Rex Perkins, Medical College, University of Alabama, for his comments and surgical advice.

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PROLONGED NEONATAL ANOXIA WITHOUT APPARENT ADVERSE SEQUELAE

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THE capacity of fetal and neonatal subjects to withstand greater degrees of hypoxia and for longer periods of time than adults is well recognized. The adult human who has stopped breathing or has otherwise been totally deprived of oxygen for 7 to 8 minutes does not survive without sustaining severe irreversible brain damage. However, there have been frequent reports of newborn infants who have survived longer periods of anoxia without recognized sequelae. Although perinatal anoxia and hypoxia have been cited as major causes of certain anatomic lesions of the brain, cerebral palsy, mental retardation, and other neurologic sequelae,[1-3] the evidence to substantiate these adverse effects of anoxia in the newborn infant is largely inferential.

The longest recorded periods of time that newborn infants have survived without apparent adverse sequelae are 140 minutes without breathing[4] and 30 minutes without a cord pulse.[5] In each instance, however, the presence of a demonstrable heartbeat provided the encouragement to continue resuscitative procedures. These infants cannot, therefore, be considered to have survived "total anoxia." The present report concerns a prematurely newborn infant who survived a prolonged period of asphyxia with no demonstrable heartbeat. Although the duration of "total anoxia" was longer than has been recorded for any surviving infant, no adverse sequelae are apparent at this time.

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CASE REPORT

A Negro boy, now 20 months of age, was born prematurely to a primigravida, nulliparous, 19-year-old Negro woman after a gestation period of approximately 35 weeks. The mother's labor was spontaneous and precipitous, being accomplished with the aid of "low forceps." No ante-partum sedation or analgesia was used. Fetal heart sounds were heard until near the time of delivery and a viable infant was expected. However, an infant weighing 3 pounds and 4 ounces was delivered who had no manifestations of life; i.e., no heartbeat, respirations, pulsation of the umbilical cord, or movement of voluntary muscles. Resuscitation was started immediately, using a mouth-to-endotracheal-tube technique, wherein the operator breathes oxygen-enriched air and in turn rhythmically inflates the infant's lungs via the endotracheal tube. This procedure was carried out for 15 minutes, at the end of which time he was declared "stillborn" because no sign of life had been or could be detected.

The infant was prepared for the morgue and was wrapped in a shroud. However, instead of being delivered to the morgue, the body was taken to a nearby room for demonstration of resuscitative techniques. The demonstration was started 25 minutes after the infant was born. An endotracheal tube was inserted and the lungs were

inflated by the expired air of 3 separate operators. Thirty minutes after delivery a pulse was first detected in the umbilical cord. A stethoscope was then placed on the baby's chest and a slow, irregular, weak heartbeat was heard for the first time. Resuscitation was continued with the technique initially used and 30 mg. of caffeine sodium benzoate was administered intramuscularly. The infant first gasped at the age of 40 minutes and began to breathe regularly and spontaneously at the age of 60 to 65 minutes.

The baby was then transferred to an Isolette with oxygen (38 volumes per cent) and received additional supportive care consisting of gavage feeding and antimicrobial therapy (chloramphenicol). After the first week, special premature infant care became unnecessary because the infant was "hardy," and his course during the remaining 5 weeks in the nursery was characterized by steady growth and development. At no time did he have seizures or detectable jaundice.

The infant's growth has been consistent and adequate in relation to his birth weight; at 20 months of age his weight and length are within the twenty-fifth and fiftieth percentiles, respectively. He appears to be a normal toddler without any neurologic defects. He is a calm child with no abnormal motions of his hands and with no hyper- or hypotonia. He developed a social smile at 2 months of age, held his head steady at 3½ months, sat alone at 8 to 9 months, pulled to a standing position at 11 to 12 months, walked alone at 15 months, and used 4 to 5 words at 16 to 17 months of age. At 20 months he is very sociable, runs and seldom falls, dumps a pellet from a bottle, scribbles with a pencil, points to pictures, uses 7 to 10 words, is beginning to use words in pairs, and responds to simple directions; however, he does not build a tower with cubes nor perform well on the form board. Formal developmental testing was carried out at 12 and 17½ months of age using the standards of Gesell and Amatruda[6] and at 20 months using the standards of Cattell.[7] On each occasion he was thought to have average development. However, it is appreciated that more subtle manifestations of brain damage such as specific learning defects may not be recognized at this age. In addition, a P.G.S.R. audiometric examination and an EEG, obtained at the age of 20 months, were interpreted as normal.

DISCUSSION

Adequate longitudinal studies defining the anoxic and hypoxic insult that newborn infants can tolerate without sustaining permanent damage to the brain are lacking, and most reports concerning the effects of hypoxia have been of a retrospective or anecdotal nature. The anoxic limit, however, has been defined in several experimental animals. Fazekas, Alexander, and Himwich[8] studied adults, infants, and fetuses in utero of various animals under oxygen-lacking conditions. Their observations revealed that mature animals survived for approximately 3 minutes after breathing undiluted nitrogen, while the average survival time of a newborn animal varied from 7 minutes in the guinea pig to 50 minutes in the rat. These investigators related the differences in survival times between the newborn of different species to differences in maturity at birth.

The survival of the anoxic newborn infant is probably dependent upon the enhanced ability of the brain at birth to utilize an anaerobic type of glycolysis. This phenomenon was first suspected when it was shown that the metabolic rate, as measured by oxygen uptake, within the immediate neonatal period is lower than it is in the adult. This difference is substantiated by studies which demonstrate that the

breakdown of carbohydrate in premature and full-term newborn infants reaches an end point short of that of carbon dioxide and water. Himwich and colleagues[10, 11] used sodium fluoride and sodium iodoacetate as enzyme poisons to interfere with the breakdown of carbohydrates; under these conditions rats were more susceptible to a lack of oxygen. Studies by Wilson and co-workers[12] have shown that acidosis in young infants, manifested by low serum carbon dioxide content and low serum pH determinations and the production of an end product other than carbonic acid (such as lactic or pyruvic acid), is an indication of anaerobic metabolism. The ability to derive cerebral energy for long periods of time in this manner is lost soon after birth.[13, 14]

Although the role of anaerobic metabolism is most probably the critical factor protecting the newborn infant from, or permitting the reversibility of, changes induced by anoxia, other factors are operative. The most important of these are the persistence of circulatory function and reduction in body temperature. It has been shown that circulatory function of some degree must be maintained if revival of a profoundly anoxic animal with respiratory failure is to be accomplished.[15] Cerebral oxygen uptake and blood flow studies have not been performed in the asphyxiated newborn infant, but in older infants and children cerebral oxygen consumption and functional activity have been correlated.[16] Alterations in body temperature occur at birth[17, 18] and there is considerable evidence that reduced body temperature ameliorates the effect of anoxia neonatally. Miller and Miller[19] have demonstrated in asphyxiated guinea pigs a linear increase in the time of survival of approximately 50 per cent per 10° C. decrease in body temperature when compared to noncooled controls. The explanation[20] offered for this observation is that the cellular metabolic rate decreases with decreasing temperature, thus reducing the oxygen requirement. In the case reported here the first body temperature (rectal) recording was obtained at the age of 12 hours and was 95° F. (35° C.). Although the infant's temperature was probably "reduced" prior to being revived and during the first hours of life, his actual body temperature probably did not approach the extreme levels of cold (20° C.) that have been used in animal experiments. Recently, extreme cold (23° to 30.4° C.) has been employed with some apparent success in conjunction with other resuscitative measures in reviving apneic newborn infants, and it may prove to be a resuscitative adjunct.[21]

Admittedly, it is an accident that this patient is alive today after having survived an unprecedented, prolonged period of anoxia. He had no heartbeat, demonstrable by auscultation, during the first 15 minutes of life; 2 trained observers listened carefully for its presence throughout this period. A period of 10 minutes elapsed between the time that he was pronounced dead and resuscitation was resumed. Although he was assumed to be dead when resuscitation was reinstituted for demonstration purposes, it is not certain whether a heartbeat might have been audible during this interim. It is perhaps important that the same observer who pronounced the baby dead detected the first signs of life 30

minutes after birth, and it was he who heard the first heartbeat with the same stethoscope used at the time of birth.

A heartbeat has always been observed in all neonatal infants who have been reported to have survived prolonged periods of anoxia. Even in the infant reported here it is probable that there was some cardiac activity even though it could not be detected. Such a situation has been reported in an elderly, obese adult in whom no heartbeat was audible for a period of 90 minutes before cardiac massage was begun, but in whom there was electrocardiographic evidence of ventricular tachycardia with intermittent fibrillation.[22] The possibility that this phenomenon might occur on occasion in apparently stillborn infants has been suggested as a reason for cardiac massage when the possibility of viability exists. The first successful cardiac massage in an apparently stillborn infant was reported in 1957,[23] and Epple and Sutherland[24] have established arbitrary criteria for the selection of stillborn infants who will receive cardiac massage in their clinic.

The survival of an infant without apparent adverse sequelae is an unusual occurrence. It demonstrates the need for evaluation of resuscitative techniques and of the length of time which they should be employed. Several recent studies[25-27] have failed to indicate an apparent correlation between delayed oxygenation of the newborn infant and intelligence or other neurologic sequelae in later life. There must be a limit, however, of the length of time which a newborn infant can tolerate anoxia without sustaining irreversible cerebral damage, even though this limit has not been defined.

SUMMARY

1. An infant is reported who survived prolonged anoxia for at least 15 and probably for 30 minutes and in whom harmful sequelae are not apparent at the age of 20 months. This period of "total anoxia" is longer than has been previously reported in surviving infants.

2. The mechanisms which permit the newborn infant to survive prolonged periods of anoxia are discussed.

I wish to acknowledge the assistance of Dr. Henry W. Baird III who examined the patient neurologically at the age of 20 months and who interpreted the EEG, Miss Marguerite V. Eversden, audiologist, who performed the P.G.S.R. audiometric examination, Dr. Milton Sarshik who performed the Gesell developmental examinations, and Dr. Gerald H. Zuk who performed the Cattell Intelligence Test.

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THE CLINICIAN AND POTASSIUM METABOLISM

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I HAVE chosen to review some aspects of potassium metabolism. This is a subject in which both clinicians and laboratory workers have made contributions, each indispensable to the other. The discontent of physicians faced with clinical observations they didn't understand led to quantitative measurements which led to the formulation of physiologic concepts, and thus to therapy. The shortcomings of these concepts and schemes of treatment have been assessed by further clinical observations.[1] In addition, this subject illustrates some aspects of the role of concepts in science and the value of thinking in terms of basic principles, both in teaching and in the intelligent practice of medicine. Finally, a review of the subject of potassium in cellular economy and the clinical manifestations of potassium deficit will induce most of us to view our daily clinical experiences with fresh perspective and insight.[2]

For a century the recurring transient paralyses experienced by several members of a family were recognized as a distinct clinical entity.[3] In 1902, one of the patients, "an intelligent, well-educated woman, made for herself the observation that citrate of potash in good sized doses would cut short an attack."[4] Purely from clinical observations on his 3 patients and from a study of the reactions to electrical stimulations, Buzzard,[5] in 1901, came startlingly close to the answer when he concluded that "a chemical or physical change in the muscle plasma alone is the probable explanation of the loss of contractility." However, Buzzard also knew, as all clinicians eventually learn, that "a true knowledge of the pathology of family periodic paralysis is essential before we can hope to secure amelioration or cure for the sufferers."

In the first quarter of this century surgeons were puzzled by the symptom complex appearing in the postoperative period in their biliary patients. Whipple[6] described the complex as pancreatic asthenia in 1923. He stated that the major features were pronounced languor and apathy, weakness, anorexia, and fall in blood pressure. "Asthenia, as severe as in Addison's disease, is the chief complaint" and is "objectively manifested by the muscular relaxation, the weakened grip." Anorexia was a constant symptom. Vomiting, prominent in all cases, was often marked, and tympanites was present. The surgeons noted the onset of symptoms on the second to ninth postoperative day when the patient, having recovered from the operation, was apparently doing well. The symptoms cleared abruptly with the intake of food. "... the change for

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Presented as The Journal of Pediatrics Educational Foundation Lecture at the Children's Hospital of the District of Columbia, April 6, 1959.

the better is often surprisingly abrupt, appearing with the return of appetite and relish for food."

In patients with vomiting from pylorie stenosis or from intestinal malrotations, the alkalosis which persisted after relief of the obstruction until food was taken was equally puzzling in the 1930's.

In diarrheal disease of infants the term "decomposition" was certainly prophetic and indicates how close to the answer some of the pediatricians of the last century were.[7] The excessive loss of body potassium was well documented by Butler, McKahnn, and Gamble[8] in 1933. Robinson[9] in Tel Aviv, in 1939, studied "the wanderings of potassium" and noted that the prognosis of acute gastroenteritis varied with the concentration of potassium in the serum. Table I illustrates the relationship he discovered in his patients.

TABLE I. SERUM POTASSIUM VERSUS MORTALITY IN DIARRHEAL DISEASE

SERUM POTASSIUM (MILLIEQUIVALENT PER LITER)	DIED	LIVED	MORTALITY (PER CENT)
-2.0	12	0	100
2.1-2.5	3	1	75
2.6-3.5	6	11	35
3.6-5.7	0	7	0

In China "Pa Pin," transient paralysis, clinically similar to familial periodic paralysis, was noted during recovery from cholera. The Chinese physicians knew that familial periodic paralysis responded to potassium, so they administered 2 or 3 per cent solutions of potassium chloride intravenously and reported dramatic and abrupt relief of the paralyses in their patients, although they were at that time unaware of the current knowledge of potassium metabolism in diarrheal disease.[10]

In still another area clinical observations and astute reasoning by analogy set the stage for a true understanding of potassium metabolism. Kepler,[11] in 1933, noted persistent alkalosis and tetany in one patient and muscular paresis in another, each having enlarged adrenal glands at autopsy. McQuarrie and associates,[12] four years later, contrasted the serum electrolyte values in a patient with adrenal hyperplasia with patients with Addison's disease. A most competent beginning of the understanding of the pathologic physiology of Addison's disease had already been made by Loeb and co-workers.[13, 14] McQuarrie further determined that the hypochloremic alkalosis and the decreased serum potassium concentration were made more abnormal by adding salt to the diet or by the administration of adrenal cortical extract, and were brought to normal values by giving an additional 10 Gm. of potassium chloride daily. His patient reported that she felt better after 5 days of potassium chloride therapy.

Thus, these and other clinical situations forced attention on potassium metabolism and produced an intellectual atmosphere in which basic studies of the anatomy and function of cellular electrolytes were quickly correlated with clinical syndomes.

For the past half century the thoughts on electrolyte metabolism had been influenced by two concepts now known to be erroneous: first, that the cell walls were impermeable to sodium and potassium, and second, that only disturbances in extracellular fluids were accessible to treatment. These theories illustrate what Conant has described as "the power of an old concept to prevail against contradictory evidence." As is so often the

ease in science, unfettered speculation by workers with creative ability combined with new methods of observation led to a reorientation of our concepts. A major share of the credit belongs to the able clinician and laboratory worker, D. C. Darrow. As Cushing stated: "No idea is wholly new; what is new is getting people to adopt it and act upon it. Credit goes to him who convinces his contemporaries." The new methods of observation were: (1) direct determination of the body composition in animals, (2) metabolic balance studies in humans, and (3) more recently, isotope diffusion studies. It is now generally accepted that disease may alter not only the composition of the extracellular fluids, so beautifully described by Gamble, but also the composition of the cells.

Possibly the easiest way to visualize the fundamental principles of cellular electrolyte metabolism is first to imagine a single cell floating in the pre-Cambrian ocean. Here the "extracellular" environment, due to its tremendous size, is constant in composition, the removal of nutrients and the excretion of wastes by the single cell having no influence on it, and the movement of the cell through the ocean furnishes all the circulation needed. The next step was for the cell to wrap around itself a small amount of the ocean and leave the sea for the land. In order to maintain the constancy of its now small amount of extracellular fluid, elaborate mechanisms had to be set up: vast portals of entry, the gastrointestinal tract and the lungs to bring in essential metabolites; a transportation system to circulate foods and wastes to and from each cell; a competent disposal system, the lungs and kidneys had to be evolved. To put the fine adjustment on these complex inter-relationships of intake, outgo, internal distribution and exchange, a system of regulators, the adrenal cortex and the osmoreceptor, hypothalamic and antidiuretic systems, were added. This imaginary model allows us to visualize all of the important basic features concerned with cellular electrolyte metabolism.

To form a human being, an extensive, complex arrangement of cells had to be assembled and this produced a lack of homogeneity and varying rates of turnover of substances which, along with inherent variations in biologic material, make accurate measurements of the extra- and intracellular composition impossible. However, a gross, but useful, simplification of the anatomy of the body fluids suffices for most clinical problems.

The usual complement of potassium within the cells is essential for normal cellular function. Under certain abnormal circumstances almost one half of the cellular potassium may be lost. Therefore, it is important to consider how potassium depletion may occur. Abnormal losses of potassium usually result from one of six mechanisms:

1. Whenever the potassium balance becomes negative due to decreased dietary intake or as the result of abnormal losses from the gastrointestinal tract or from renal dysfunction, potassium is lost. Low or zero intake may be produced by anorexia or nausea from illness and is present in those patients maintained on parenteral fluids which contain no potassium.[15] All gastrointestinal fluids contain potassium and therefore losses of these fluids by vomiting,[16, 17] or escape of fluids through fistulas or by the aspiration of the stomach or upper

intestinal tract,[18] or from diarrhea[19] may produce potassium depletion. In many cases major outgo of potassium from the body is in the urine[20] but, in most instances, such excretion is secondary to other changes. Primary renal disease which produces a loss of potassium is not frequent,[21] but renal loss of potassium does follow the administration of some diuretics.

2. An inability of the cells to maintain their high concentration gradient of postassium owing to depressed metabolism, causes potassium depletion. Clearly some important regulation exists within the cells. Apparently the high cellular concentration of potassium is dependent upon the energy derived from aerobic oxidation or anaerobic glycolysis.[22] Any decrease of metabolic activity produces a loss of potassium and an increase of sodium within the cells. Clinically, in any situation wherein "shock" due to trauma, burns or cold,[23] impaired "effective" circulation, or anoxia is present, a loss of potassium from the cells may result because their metabolic activity is decreased.

3. Adrenocortical hormones, especially aldosterone, acting both on the cells directly and also on the renal tubules tend to raise the cellular content of sodium and to cause a loss of potassium from the cells. Adrenocortical tumors,[12] aldosterone-producing tumors,[24] the administration of ACTH, cortisone, desoxycorticosterone acetate, or related steroids,[25] and the naturally occurring "stress" accompanying illness, for example, in surgical procedures [26, 27] and in diabetes,[28] will tend to decrease cellular potassium.

4. Changes in hydrogen ion concentration of the extracellular fluid is another way in which the potassium level is altered. The cellular content of potassium varies inversely with the pH of the serum; the intracellular sodium varies directly with the serum pH. Conversely, if the primary alteration is a deficit of cellular potassium, the dynamic equilibrium reached is an elevated serum pH, and a metabolic alkalosis, which will persist until the cells have regained their usual amounts of potassium.[29]

5. Dehydration in the presence of appreciable renal function will lead to a loss of cellular potassium.[30]

6. Finally, the reciprocal relationship between high sodium intake and increased potassium excretion, first noted by Bunge and reinvestigated by Gamble, may produce potassium deficit, particularly from the injudicious clinical use of sodium salts orally or parenterally.[31]

The clinical diagnosis of significant losses of body potassium depends upon two factors:

1. "anticipating" the possibility of potassium deficits whenever the clinical condition encountered might set into operation any of the six mechanisms just mentioned;

2. whenever one observes any signs of dysfunction of cardiac, skeletal, or smooth muscle functions, nervous system changes, or biochemical abnormalities. Frequently these clinical signs are obscured by the presence of other abnormalities at the onset of treatment and become more apparent after partial correction of the pre-existing deficits in the extracellular compartment. Table II lists the symptoms and signs most frequently observed in potassium deficiency without decreased fluid volume.[32] Usually only a few of

the features, often in only one category, are found in an individual patient. Additional clues to the presence of potassium deficiency are: (1) the failure of patients to gain in strength and sense of well-being or the persistence of metabolic alkalosis following therapy, adequate except for potassium, and (2) the observation of prompt improvement when adequate potassium has been administered.

TABLE II. SYMPTOMS AND SIGNS OF POTASSIUM DEFICIENCY

Nervous system	
Mental state	Weakness, lethargy Apprehension Depression, confusion
Reflexes	Depressed
Cardiovascular system	
Heart	Tachycardia Sounds of poor quality Enlargement Appearance of murmurs Appearance of congestive failure
Blood pressure	Widening of pulse pressure Hypotension
Pulse	"Corrigan's" pulse Irregular rhythm
Veins	Elevated venous pressure
Respiration	Shallow, gasping respirations Dyspnea, cyanosis
Gastrointestinal tract	Nausea, vomiting Abdominal distention Paralytic ileus
Muscles	Muscular weakness Soft, flabby, hypotonic muscles Flaccid paralysis
Laboratory abnormalities	
Electrocardiogram	Lowered, flattened, or inverted T waves U waves Depressed S-T segments Extrasystoles, A-V block
Serum concentrations	
pH	Elevated
HCO_3	Elevated
Cl	Decreased
K	Lowered in presence of good renal function
Serum proteins	May be lowered
Glucose	Hyperglycemia or decreased glucose tolerance may be present

CONCLUSIONS

Once a new concept has been formed, its effectiveness is soon demonstrated by the discovery of new facts and new relations[33] both forward and, paradoxically, backward in time. Thus, in the light of a new concept past observations take on a new significance.[34] Certainly the new concept of cellular physiology is no exception. The puzzling clinical syndromes mentioned in the beginning of this paper are, at least partially, explained. The application of our current knowledge of electrolyte physiology has contributed much to the lowered mortality of diarrheal disease, to the success of recent surgical procedures, to the safer use of adrenal steroids, and even to the more adept use of such "old" drugs as digitalis[35] and mercurials.

The image of the single cell in its pre-Cambrian ocean is useful because it aids us in thinking about basic principles of cellular composition and the regulatory mechanisms. The knowledge of a few basic principles enables the clinician to recognize physiologic derangement, in this instance, potassium deficiency, in many illnesses without the burden of trying to remember minute details of every clinical condition. Similarly, he can individualize his fluid therapy instead of memorizing as many "fluid routines" as there are diseases.

Wise physicians eventually learn that a doctor treats patients and physiologic *disturbances in patients* rather than diseases.[36] Also, they come to

realize that most of the satisfaction derived from the practice of medicine is an intellectual one, it comes from understanding "what is the matter with the patient and how to correct the abnormal dysfunctions" or from efforts to gain new valid information where only speculation or prejudice now exist. It is for these reasons that the "potassium story" is such a favorite of mine.

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"In a disease whose tendency is so little generally understood, and which is so alarming and distressing in its manifestations, the ultimate issue of the case is often a subject of the most painful anxiety to the sufferer and his friends; it is therefore a matter of some importance that the physician should be able to detect the tendency of the disease in any given case, and to form something like a definite prognosis. . . .

"If the patient is young, the chest sound, the attacks short, the intervals long; if there is no permanent shortness of breath, no cough or expectoration; if the attacks are getting milder or rarer, and if the exciting cause is clear and such as may be obviated, then a favourable prognosis may be given. . . ."

The Prognosis of Asthma, by Hyde Salter, M.D.
From the British Medical Journal, June 18, 1859.

ENTERITIS DUE TO ENTEROPATHOGENIC ESCHERICHIA COLI

Present-Day Status and Unsolved Problems

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DURING the past decade it has been established that certain serologic types of *Escherichia* (E.) *coli* are enteric pathogens. Numerous papers on *E. coli* enteritis have appeared in the scientific literature of many countries. It is the purpose of this review to summarize briefly and critically the facts that have emerged from these investigations, to discuss the practical applications to the diagnosis, treatment, and prevention of this malady, and to point out the unsolved problems.

ENTEROPATHOGENIC ESCHERICHIA COLI ENTERITIS

Enteropathogenic *E. coli* (E.E.C.) enteritis is an acute infection associated with diarrhea and frequently with vomiting and fever. It is prevalent among infants under 2 years of age. The incubation period varies from 2 to 12 days. Relapses are common unless the patients are treated. Clinically, the disease is not sufficiently different from enteritis due to other causes so that the diagnosis depends on bacteriologic examination. The disease is highly contagious among infants. Sporadic infections are more common than was hitherto assumed. Neomycin and certain other antibiotics are strikingly effective, both therapeutically and prophylactically. Measures for the prevention and control of epidemics have been established.

ETIOLOGIC AGENT

E. coli is a normal inhabitant of the intestinal tract of man and indeed, of all mammals. Outside the digestive system it is capable of causing infection. On the basis of antigenic structure, this species can be divided into a large number of serogroups and serotypes. It has been clearly established, largely through the pioneer work of Kauffmann,[1] that *E. coli* contains three principal kinds of antigens, referred to as O, K, and H antigens. The O or somatic antigen characterizes the serologic group. At the present time, 140 such antigens have been recognized and there exist, therefore, 140 serogroups. The O antigen is made up of polysaccharide, lipid, and protein; this complex possesses toxic and pyrogenic activity and is frequently referred to as endotoxin. It is the polysaccharide moiety which gives this complex its serologic specificity and, according to the important studies of Westphal and associates,[2] it is the lipid which endows it with its toxic capacity. The second type of antigen characterizing this species is referred to as K antigen. Three different kinds of K antigens

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The author's research incorporated in this review was aided by research grants from the National Institute of Allergy and Infectious Diseases, U. S. Public Health Service.

exist, the so-called L, A, and B antigens, the latter being of prime importance with regard to enteritis strains. At the present time it is not definitely known whether the B antigens are distinct molecules present in the bacterial cell wall or whether they merely are a serologically active part of the O antigen. The third major antigen of *E. coli* is the flagellar or H antigen, present only in motile strains. The K and H antigens within each serogroup characterize the various serotypes.

Among the 140 serogroups and almost innumerable serotypes of *E. coli*, less than 10 per cent are etiologically related to infantile enteritis. In view of the fact that apparently all groups and types of *E. coli* are potentially pathogenic outside of the intestinal tract and only a certain few are associated with enteritis, the term enteropathogenic *Escherichia coli* (E.E.C.) has been suggested for the latter.[3] This term corresponds to "Dyspepsie-coli" used by the Germans. For the disease, Young[4] has suggested the term "colienteritis."

The following serotypes of E.E.C. have been recognized, as summarized by Ewing and colleagues[5]: 026:B6, 055:B5, 086:B7, 0111:B4, 0112:B11, 0119:B14, 0124:B17, 0125:B15, 0126:B16, 0127:B8, 0128:B12. For a more modern terminology of B antigens and additional information on E.E.C., the interested reader is referred to Ewing and co-workers.[5] Other serotypes of E.E.C. may well be discovered in the future. For example, in Egypt enteritis associated with *E. coli* 020 has been observed.[6] Before accepting new serotypes as enteropathogenic, careful clinical, etiologic, and epidemiologic studies are needed; it is desirable also to obtain information on experimental production of the disease and on the antibody response of patients with natural and experimental infections.

E.E.C. may be subdivided further according to biochemical activities (sugar fermentation, etc.) of the strains into biotypes, to susceptibility to bacteriophages into phagetypes, and to susceptibility to colicines (antibacterial substances) into colicinotypes. The latter were studied by Hamon.[7]

Convincing proof of the etiologic role of E.E.C. in enteritis of infants is available for several serotypes, notably 0111:B4, 055:B5, and 0127:B8. (1) In patients with the infection, E.E.C. can be detected in the majority of cases, and often as the predominating microorganism among the gram-negative bacillary flora. (2) E.E.C. is only rarely encountered in healthy infants, children, and adults, unless they were exposed during an outbreak. (3) Human volunteer experiments have demonstrated the pathogenic potentiality of E.E.C. in contrast to "normal" strains. (4) During the experimental disease, E.E.C. can be reisolated from the subjects. (5) Patients with natural E.E.C. infection and volunteers after ingestion of this microorganism may develop specific antibodies. (6) Certain antibiotics, notably neomycin, are effective clinically and bacteriologically, whereas favorable results would not be expected in virus enteritis. (7) In a number of outbreaks of E.E.C. enteritis no other pathogenic bacteria or viruses were isolated. It is clear, therefore, that Henle-Koch's postulates

have been fulfilled for E.E.C. as convincingly as for shigellae and salmonellae. This evidence is not as complete for several of the other serotypes mentioned above.

It is likely that other serotypes of *E. coli* are responsible for diseases other than enteritis. Ewing and associates[8] reported on the association of serogroups 0138 and 0139 with edema of swine. It remains for the future to establish such relationships on a broader basis and to determine the factors in various serotypes of *E. coli* operative in the production of various disease entities of man and animals.

PATHOGENESIS

Of all the facets of E.E.C. enteritis, none is as poorly understood as the pathogenesis. To a large extent, this is due to the failure to reproduce the human disease in experimental animals. De and associates[9] reported that injection of certain strains of *E. coli* into ligated loops of the small intestine of rabbits resulted in dilatation; this effect was produced by 22 of 40 strains from patients with acute or chronic diarrhea, but only with 3 of 20 strains isolated from healthy individuals. Taylor and co-workers[10] studied the effects of two strains of *E. coli* in male rabbits of the Copenhagen strain and found that dilatation and purulent inflammatory changes were produced in the gut segments by injection of the pathogenic strain, but the control strain usually failed to produce these reactions. Similarly, McNaught and Roberts[11] reported that 13 of 16 strains from patients with gastroenteritis produced lesions, whereas only 1 of 7 strains isolated from healthy individuals did so. It will be important to learn whether strains of *E. coli* freshly isolated from extraintestinal infections such as pyelitis and peritonitis yield positive results, and also to discover the basic differences between strains of the identical serotypes of *E. coli* which do and those which do not produce lesions in the intestinal segments of rabbits.

Experimental infection in human volunteers has been produced by several investigators, including Ferguson,[12] Hiroki, Koya and associates,[13] and Neter and Shumway.[14] "Normal" strains did not produce diarrhea. Koya and associates[15] found that administration of *E. coli* 0111:B4 into the ascending colon failed to produce enteritis and concluded that clinical manifestations of E.E.C. enteritis were due to multiplication of the microorganisms in the small intestine.

These are two principal questions: (1) Which factors endow E.E.C. with its capacity to produce enteritis in infants upon oral ingestion? (2) Which factors of the host render the small infant so exquisitely susceptible to this disease? So far as the pathogen is concerned, none of the antigens, which serve so well for identification, appear to be responsible for enteropathogenicity. The suggestion that E.E.C. may possess greater survival potential in tissue cultures than nonenteropathogenic strains and be more potent in producing the Shwartzman reaction has been made by Lindberg and Young.[16] Additional studies in this direction are necessary before one can accept that fundamental differences between enteropathogenic and nonenteropathogenic *E. coli* can be detected by these methods. It will also be interesting to learn whether a relationship exists between these characteristics of E.E.C. and its ability to

produce lesions in the rabbit gut. Braun,[17] who has carried out extensive investigations on *E. coli* enteritis in Germany, found that the endotoxins are adsorbed by epithelial cells of the small intestine of cats. Whether this attachment plays a role in the development of the natural disease in man is unknown at this time. Smith and Thomas[18] made the interesting observation that endotoxins are lethal to the chick embryo and that 10-day-old embryos are more susceptible than younger and older embryos. The determining factors accounting for this age difference in susceptibility remain unknown.

The role of both pathogen and host in the development of clinical manifestations of enteric infection in general is strikingly illustrated by the observation of Watt and colleagues[19] to the effect that, in contrast to many other outbreaks, salmonellosis in a premature infants' nursery was unaccompanied by diarrheal disease. An intriguing hypothesis on the pathogenesis of E.E.C. enteritis has been suggested by the Hungarian workers, Eörsi and associates,[20] namely, that bacteriophage must be present together with E.E.C. to cause illness. This theory should be explored further. It has been frequently observed that certain serotypes of E.E.C. are more apt to spread from infant to infant than are others. For example, *E. coli* 0111:B4 and 0127:B7 possess greater capacity in this respect than serotype 026:B6.[21] The reasons for these differences are not understood.

Elucidation of the pathogenesis of this infection requires intensive studies of the host factors. It has been clearly established that the disease occurs predominantly in infants under 2 years of age and is rarely encountered in older children and adults.

Antibodies against E.E.C. are present, though in relatively low titers, in the blood of almost all adults.[3] The reasons for the development of these antibodies are not entirely clear. Some scientists are of the opinion that certain "normal" antibodies develop without antigenic stimulation; others consider it more likely that all antibodies are the result of the stimulating effect of antigens. It is important to keep in mind, particularly with regard to O antibodies against enteric bacteria, that similar antigens may be encountered in unrelated microorganisms and even in other materials and that the antigens are heat resistant and may be introduced into the intestinal tract in the absence of living microorganisms. That E.E.C. at one time or another is present in the absence of overt disease in many individuals is strongly suggested by the findings of Gamble and Rowson[22] who calculate that 1 to 2 per cent of the population harbor E.E.C. at any one time.

It has been shown that antibodies against the somatic antigens of E.E.C. are poorly transferred through the placenta from mother to newborn infant and that these antibodies often make their appearance after the first year of life.[3] Although it would be tempting to postulate a cause and effect relationship between susceptibility and absence or low titers of these antibodies, no information is available to support this concept. It will be necessary also to learn whether antibodies against these strains are

present in the intestinal tract (coproantibodies) of older children and adults and whether they are protective. Incomplete E.E.C. antibodies have been demonstrated in some specimens of cord serum.[23]

The contribution of breast feeding to resistance to E.E.C. enteritis has not been explored fully. A number of authors have reported that bottle-fed infants are more susceptible to E.E.C. enteritis than breast-fed infants.[24, 25] E.E.C. enteritis does occur, however, in breast-fed infants, although in the experience of Brown and Bailey,[26] severe enteritis has not been observed in them. Interestingly, Lindberg and Hunter[27] demonstrated high titers of E.E.C. antibodies in colostrum by means of the hemagglutination procedure, but at present no definitive information is available as to whether these antibodies are protective and whether they are absorbed in the gastrointestinal tract. The potential danger of nonsterilized breast milk in milk banks has been clearly demonstrated by Mossel and Weijers.[28]

Steigman and Lipton[29] demonstrated antibodies against polioviruses in amniotic fluid. In one of their specimens antibodies against various enteric bacteria, including E.E.C., were demonstrated. Further studies are needed to determine how frequently E.E.C. antibodies are present in human amniotic fluid and whether they contribute to resistance of the newborn infant.

The extraordinary susceptibility of the young infant to E.E.C. may be related to the absence or deficiency of factors other than antibodies contributing to resistance of the older child and adult. Unfortunately although much has been learned our understanding of such factors as properdin and lysozyme is quite inadequate. Even the role of the normal bacterial flora in resistance to enteric infections is not clarified. Bacteria producing antibiotics may or may not be present in the intestinal tract, and in a single individual a continuous change in this flora may occur.[30] Research on "germ-free" animals has been carried out in several laboratories, including those at Notre Dame University and Walter Reed Hospital and in Sweden. Wagner[31] showed that germ-free chicks not exposed to *E. coli* failed to develop antibodies against this species, although antigenic stimuli engendered such antibodies. It is also of interest to note that striking differences exist in the morphologic features of the gastrointestinal tract between germ-free and conventional animals.[32] Amano, Goebel, and Smidth[33] made the interesting observation that colicine activity is associated with the O antigen of *E. coli* and, more specifically, with the protein moiety.

As a guide to the elucidation of the pathogenesis of E.E.C. enteritis, it may be pointed out that host resistance may be altered experimentally. For example, Formal and co-workers[34] succeeded in producing enteric infection in guinea pigs with a strain of *Shigella flexneri* 2a, provided that the animals fasted for 4 days and that calcium carbonate was administered before, and opium following, the challenge infection. Host resistance of animals to experimental shigella infection can also be decreased by nonspecific physical stress and to a lesser degree by fatigue.[35] Similarly, overeating plays an essential part in the development

of *Clostridium welchii* type D enterotoxemia of sheep.[36] It has been the impression of many clinicians that such host factors play a striking role in the development of E.E.C. enteritis and its severity. Enteritis may be triggered by an upper respiratory infection or by a dietary insult. Further investigations into these resistance influencing factors are needed.

It is remarkable how infrequently extraintestinal infections due to E.E.C. are encountered in infants with or without enteritis. However, a few such cases have been reported; for example, meningitis has been described by Fayot-Petitmaire and colleagues.[37]

CLINICAL FEATURES

E.E.C. enteritis is encountered primarily in infants under the age of 2 years. Outbreaks have occurred among infants in many hospitals and other institutions. The incubation period shows considerable variation possibly depending upon the infecting dose, virulence of the strain, degree of susceptibility of the host, and other factors. It ranges from 2 to 12 days. In experimental human infection it may be as short as 7 to 24 hours.

The disease may be fulminating, severe, or mild, and subclinical infections are common in institutions. In addition to diarrhea, fever and vomiting are frequently present. E.E.C. enteritis does not present clinical features sufficiently characteristic to warrant a specific diagnosis on clinical grounds only. A thorough analysis of the various clinical manifestations of enterobacterial infections including E.E.C. enteritis, has been published by Oeklitz and co-workers.[38] Cooper and associates[39] noted abdominal distention in infants with 0127:B8 enteritis and a characteristic unpleasant odor of the feces. Hinton and MacGregor[25] did not observe these features. The development of E.E.C. enteritis may be induced by extraintestinal infections or dietary inadequacies. Herweg and associates[40] found concurrent extraintestinal infection in 36 per cent of patients with E.E.C. enteritis. Practically all complications arising from severe diarrhea, no matter what the infecting microorganism, are encountered in E.E.C. enteritis. Fatality rates of E.E.C. enteritis have been reported as varying from 0 to more than 50 per cent.[41] This variability may be due to several factors: (1) the virulence of the organism may undergo changes; (2) the resistance of the infant population may vary, as, for example, in premature and full-term infants; (3) the management of dehydration, acidosis, and other complications of enteritis has improved; and (4) specific therapy is now available.

INCIDENCE

To illustrate the importance of all diarrheal diseases as a cause of death in the Americas, during a 12 month period 136,311 patients died from such infections.[42]

E.E.C. enteritis has been observed during the past decade in practically all countries where a search for this pathogen has been undertaken. It has been reported from the Americas, Europe, Australia, the Near East, India,[43] and the U.S.S.R.[44] This disease has also been encountered in the tropics[44a] and in the Eskimos of Alaska.[45] The true incidence of

E.E.C. enteritis is not known; it is not exclusively a summer disease.[46, 47]

Of particular significance are studies on the relative incidence of various bacterial enteric infections of infants. As expected, marked variations exist. Quilligan and Shadomy[48] observed a total of 106 infants with diarrhea during the summer of 1956, and found that no fewer than 36 of the infections were associated with E.E.C. Cooper and associates,[49] in a thorough investigation on the comparative frequency of various enteric pathogens, found that E.E.C. was present in more patients than salmonellae and shigellae combined. In Mexico[50] among 802 sporadic cases shigellosis accounted for 15 per cent, E.E.C. enteritis for 12 per cent, and salmonellosis for 2 per cent. A comprehensive review of acute gastroenteritis at Toronto during 1956, was carried out by Armstrong.[46] E.E.C. enteritis was recognized in only 21 of 821 cases; in contrast, 107 cases were observed during 1954. Herweg and associates[40] at St. Louis Children's Hospital found 40 per cent of enteritis cases due to E.E.C. and only 9 per cent due to shigellae. In Israel Olitzki[51] encountered E.E.C. infection in approximately 20 per cent, shigella infection in 16 per cent, and salmonella infection in 5 per cent of 101 infants with enteritis. Thomas and Charter[47] studied 1,135 children with diarrhea in London. E.E.C. was found in 8 per cent, *Shigella sonnei* in 11 per cent, and salmonellae in 3 per cent of the patients. Derham and Rogerson[52] reported that of 466 infants with gastroenteritis, 144 infections were due to E.E.C., 97 to *S. sonnei,* and 30 to salmonellae. That the presence of an outbreak influences the relative incidence of one enteric infection in relation to others is obvious. For example, Martineau and co-workers,[53] in Canada, observed 258 cases of E.E.C. 0127:B8 infections during 1956 to 1957, and only 12 cases of salmonellosis and 14 cases of shigellosis.

Dual infections with E.E.C. and with shigellae or salmonellae have been studied by several authors.[50, 52, 54] It must be emphasized that in many patients with apparent infectious enteritis no recognized pathogens are isolated. For example, Cooper and colleagues[49] in a study of 2,865 children with diarrhea observed 889 who harbored no E.E.C., salmonellae, or shigellae.

An interesting observation on simultaneous infection of twins, one of whom became a carrier while the other was gravely ill with enteritis, was reported by Hutchinson.[21] The host factors which determined this disparity remain unknown.

The role of various viruses as a cause of diarrhea in infants cannot be underestimated.[55] A convincing report on epidemic diarrhea in premature and older infants caused by Echo virus type 18 has been presented by Eichenwald and associates.[56] Ramos-Alvarez and Sabin[57] isolated a large variety of enteroviruses, including Echo, Coxsackie A and B viruses, as well as adenoviruses from approximately 50 per cent of a group of children with diarrhea. Echo viruses were recovered less frequently from children without diarrhea, but the incidence of Coxsackie and of polioviruses was similar in both groups. On the basis of antibody studies they suggested that summer diarrheal disease in young children is

frequently caused by enteric viruses. Enteric bacteria were isolated from only 22 per cent of the patients studied in contrast to enteric viruses from 44 per cent. Combined infections with bacteria and viruses accounted for 15 per cent. Young[4] reported the isolation of cytopathogenic agents in monkey kidney tissue culture from 48 per cent of 29 Puerto Rican infants with gastroenteritis; in 5 of the patients a significant rise in antibody titer was also demonstrated. Sommerville[58] isolated 75 enteroviruses from 338 children with diarrhea and 17 from 115 control patients with respiratory infections. The proportion of polioviruses and Coxsackie viruses was similar in each group, but Echo viruses were isolated from a greater (although not significantly) proportion of the group with diarrhea. From the patients with diarrhea, viruses were isolated from 22 per cent and intestinal pathogenic bacteria from 36.5 per cent. In view of the fact that enteric viral disease is strikingly seasonal in incidence, while E.E.C. is not, the question may be raised as to whether and, if so, to what extent, these viruses are also responsible for diarrhea during the winter and spring. It is conceivable that during the summer months diarrhea, no matter what the cause, may be associated with a higher isolation rate of enteric viruses. Studies on the presence of these viruses after administration of cathartics would seem to be indicated. Further research should yield definitive information on the incidence and delineation of viral enteritis.

DIAGNOSIS

As emphasized by Higgins,[55] "on clinical grounds, the diarrheal disease complexes produced by bacteria, intestinal protozoa and helminths, poisonous foods or chemicals, systemic disease, or as a side-effect of antibiotic therapy, present so many variants that no more than an informed guess is possible."

The specific, etiologic diagnosis of E.E.C. enteritis can be made at present only by bacteriologic examination. To this end, fecal material or rectal swabs should be obtained as early as possible during the course of the disease and, preferably, prior to antibacterial therapy. The specimen should be seeded on blood agar and on a differential medium suitable for the growth of *E. coli*, such as MacConkey agar. Typical colonies of *E. coli* are then identified serologically. Unfortunately, a specific, selective culture medium for isolation of E.E.C. does not exist at this time. Hence, it is necessary to examine several *E. coli* colonies from each specimen. The appropriate diagnostic antisera are now commercially available. Preliminary indentification is made by means of a slide test, using polyvalent antisera containing antibodies against both O and B antigens. If positive results are obtained, the test is then performed with monovalent antisera. Since this preliminary slide test employs an unheated suspension and thus identifies only the B antigen, it is necessary to perform an agglutination test with a boiled suspension for the determination of the O antigen. This test is usually performed in test tubes with either O or OB antisera. It is important to emphasize that the strains thus studied must have the characteristics of the *E. coli* species. Needless to say, stool specimens from infants

with diarrhea should be studied also by suitable methods for the presence of other enteric pathogens such as salmonellae, shigellae, staphylococci, and others.

Certain strains of E.E.C., in contrast to many nonenteropathogenic cultures, fail to produce acid from sorbitol. Sorbitol-containing agar, therefore, has been recommended as a diagnostic culture medium. It must be emphasized that this differential culture medium should not be used routinely and exclusively for the study of sporadic cases and of epidemics, since reliance on this procedure would result in erroneous diagnoses in a substantial number of instances. However, if during an epidemic it has been shown that the incitant is sorbitol negative, this culture medium is of value for screening purposes. Quilligan and Shadomy[48] found only 25 per cent of E.E.C. isolates to be sorbitol negative.

Attempts have been made to obtain etiologic information more rapidly. Hodes[59] described a rapid test based on the detection of the O antigen present in the supernate of fecal matter. Whitaker and co-workers[60] recently described the application of the fluorescent antibody technique to the identification of E.E.C. in fecal specimens. Both procedures deserve further study, particularly with regard to sensitivity and specificity. It must be kept in mind that certain bacterial antigens are shared by unrelated species and that the demonstration of a given antigen alone does not always identify a given bacterial species, serogroup, or serotype.

The importance of repeated bacterial examinations in surveys for carriers who, in contrast to many infants with active disease, excrete relatively few E.E.C. is clearly illustrated by the study of Gamble and Rowson[22] who found 6 per cent positive when less than 5 specimens were tested and 58 per cent positive when 5 to 10 specimens were examined.

Although advances have been made in the detection of the specific antibody response of infants with E.E.C. enteritis, these procedures do not lend themselves as yet to routine use. The methods employed include agglutination tests with centrifugation to enhance the reaction[61] and the hemagglutination procedure.[62]

Mixed infections with various serotypes of E.E.C. and with E.E.C. and salmonella or shigella organisms have been reported.[50, 52, 63, 64] The mere isolation from the feces of two potential pathogens does not give unequivocal evidence of the etiologic role of either. A specific antibody response to one or another or to both of the pathogens may supply more suggestive evidence. In an infant with diarrhea who excreted both *S. sonnei* and E.E.C. the author found an increase in antibody titer only against the former, suggesting that the patient had shigellosis and was a carrier of E.E.C. Further studies in this direction are desirable and may clarify multiple enteric infections.

EPIDEMIOLOGY

E.E.C. enteritis occurs sporadically and epidemically in many parts of the world and at all seasons of the year. Outbreaks of the disease have been encountered in numerous hospitals and institutions caring for infants. Although Adam in Germany, more than

a quarter of a century ago, carried out pioneer studies on the role of certain biotypes of *E. coli* in enteritis of infants, the current epidemiologic-serologic research phase began in England in 1945. In the United States two epidemics occurring in 1947, have been investigated by the study of fecal specimens that had been kept frozen for 5 years; E.E.C. 0111:B4 was identified in all available specimens.[65] As in other infectious diseases, changes in virulence of the etiologic agent may contribute to changes in epidemiology, including severity of the illness. That such changes may take place with regard to E.E.C. has been suggested by several investigators.[21, 66]

For the practitioner it is important to keep in mind that institutional outbreaks of the disease may be initiated either by infants with clinical disease or by carriers. Convalescent carriers are not uncommon; Cooper and colleagues[49] observed a rate of 8.3 per cent. Interestingly, the salmonella carrier rate observed by them was 36.6 per cent and the shigella rate, 2.6 per cent. E.E.C. is relatively rare in healthy preschool children.[67] Thomson and associates[66] calculated that 1 per cent of infants under 1 year of age living at home harbor E.E.C. That adults do not frequently become excretors of E.E.C. was documented recently by Hutchinson[21] who observed only 1 excretor among 123 adult contacts. The excretor was a nurse. Similar observations were made by Ocklitz and Schmidt[68] and by others.

In view of the striking susceptibility of the infant, outbreaks usually occur in nurseries, infant wards, either pediatric or surgical, and homes for infants. In some of the outbreaks the morbidity rate reaches 100 per cent. In an unpublished epidemic of the disease due to E.E.C. 0111:B4 all 40 infants on two floors of a pediatric institution developed clinical illness (Neter). An outbreak of E.E.C. enteritis among infants in a nursery for surgical patients has been reported.[69]

Epidemics may arise from the transfer of an infected infant to another institution. Hinton and MacGregor[25] described an explosive outbreak of this disease in a local nursing home upon the transfer of a baby from another hospital where he had been treated for severe gastroenteritis; only 1 infant of the entire group of 19 remained unaffected. Transfer of E.E.C. enteritis from one institution to another has been studied thoroughly by Thomson and associates,[66] Stock and Shuman,[70] and others. Herweg and associates[40] made the interesting observation that a carrier of E.E.C. 0127:B8 was responsible for diarrheal infection in 22 of 123 patients with other diseases, who had to be readmitted to the hospital.

Feces containing large numbers of E.E.C. unquestionably is the main source for the spread of this pathogen. Patients with active disease frequently excrete enormous numbers. E.E.C. is readily spread through contaminated hands, gowns, and possibly by fomites.[71] The survival of this organism for many days or several weeks in dust and on furniture has been clearly demonstrated.[21] However, it is not definitely established or even likely that dust plays a major role in the transfer of E.E.C. in hospital wards. It has been shown by several investigators that E.E.C. may be present in

the upper respiratory tract of infants with enteritis, even in the absence of vomiting.[14] Laurell and colleagues[72] have carried out extensive studies on airborne infections.

The possible transfer of E.E.C. from mother to newborn baby was established by Cooper and co-workers[73] and by Ocklitz and Schmidt.[74]

Epidemiologic investigations into outbreaks are aided by the determination of the flagellar (H) antigens of E.E.C. This method was utilized by Wright and Roden[75] who could clearly show that a seemingly single outbreak of E.E.C. 055:B5 enteritis was in fact two or more outbreaks. Phage typing, colicinotyping, and other procedures may be useful in this respect.

Since cattle may harbor E.E.C. or similar organisms, the possibility of the spread of the disease through the use of unpasteurized milk must be considered.[76, 77] Thomson[78] showed that unheated cow's milk may contain E.E.C., and he suggests that summer disease of several decades ago may have been milk-borne E.E.C. infection. From a practical point of view, terminal sterilization of pasteurized milk abolishes any potential danger of E.E.C. contamination.

THERAPY

Symptomatic therapy of E.E.C. enteritis, aiming at restoration of fluid and electrolyte homeostasis, is as important as antibacterial therapy. A succinct discussion of the current status of therapy in infantile diarrhea has been presented by Cooke.[79] Only specific treatment will be discussed here.

It has been clearly established that most strains of E.E.C. are susceptible to various antibacterial agents, including chloramphenicol, tetracyclines, neomycin, polymyxin B, and Furoxone. In vitro sensitivity tests on E.E.C. have been carried out by numerous authors.[80] Cooper and associates[39] found that the comparative effectiveness of polymyxin B, neomycin, chloramphenicol, and tetracycline against *E. coli* 0127:B8 was on a decreasing basis in the order stated; the strains were resistant to streptomycin and sulfadiazine. In only two patients was a moderate increase in neomycin resistance observed following neomycin therapy. It must be emphasized that the emergence of chloramphenicol- or tetracycline-resistant microorganisms has been encountered during outbreaks; under these conditions the drug may be effective initially, but subsequent employment may result in failures. At the present time neomycin given by mouth is considered to be the drug of choice since it is generally effective and essentially free of undesirable side effects. The remarkable efficacy of neomycin (50 to 100 mg. per kilogram per 24 hours for 7 to 10 days) has been well documented by Rogers and co-workers,[81] Wheeler,[82] Stulberg and co-workers,[83-85] and others. It should be noted, however, that neomycin-resistant strains have been encountered.[53] For this reason, it is desirable, particularly during epidemics, to carry out in vitro sensitivity tests on representative isolates. Bacteriologic failures from neomycin therapy, in spite of clinical improvement, have been reported in infants whose infecting strain remained sensitive in vitro to this antibiotic. This situation is similar to that encountered in the antibiotic therapy of salmonella enteritis.

The reason why these microorganisms continue to be present after apparently intensive therapy is not clear; it is clear, however, that in vitro resistance is not the only determining factor. Perhaps it is significant that in fatal cases E.E.C. has been isolated from the gallbladder.[53]

Polymyxin B, too, has been used for the treatment of this disease.[25] This drug should be given serious consideration, particularly when neomycin-resistant E.E.C. are encountered. Like neomycin, polymyxin B is poorly absorbed from the intestinal tract. Cooke[79] suggests the combined use of neomycin and polymyxin B, based on the fact that in vitro this combination is more effective than either antibiotic alone. Framycetin sulfate (sofradmycin) has been used for the treatment of E.E.C. enteritis in a dosage of 50 mg. per kilogram per 24 hours by mouth and appears to be effective.[86] Humycin, an antibiotic resembling neomycin, was used in 20 patients, but the results were poor.[53] Furazolidone (Furoxone), an antibacterial nitrofuran, has been studied by Rogers and associates.[87] Ponce De Leon[88] reported favorable results in patients with intestinal infections due to salmonellae, shigellae, and possibly E.E.C. This drug deserves critical appraisal in the treatment of E.E.C. enteritis.

Although yogurt and similar milk products have been recommended for the treatment of intestinal disorders, a critical study on their usefulness in E.E.C. enteritis remains to be undertaken. Suggestive beneficial results have been briefly mentioned by Raffle.[89] So far as the therapeutic value of breast milk which may contain E.E.C. antibodies[90] is concerned, Svirsky-Gross[91] treated one group of premature infants with E.E.C. 0111 with breast milk and a second group with lactic acid milk and concluded that breast milk feeding exerted favorable effects.

Both complete and incomplete antibodies against E.E.C. have been demonstrated in commercial human gamma globulin[92]; whether systemic or oral administration of this material to young infants with E.E.C. enteritis is therapeutically effective remains to be determined.

PROPHYLAXIS

The prevention and control of epidemics of E.E.C. enteritis in institutions are of obvious importance. Since infection is principally limited to infants under 2 years of age, greatest attention must be focused on nurseries, infants' wards, and other places caring for small children.

The infection may be introduced into a nursery by infants with diarrhea or by carriers of E.E.C. Clearly, infants with diarrhea, if at all possible, should not be admitted to an open ward or even a "diarrhea ward." It must be appreciated that a large number of pathogens are responsible for enteric infection and that cross infection must be avoided. In most places it is not practical to isolate all infants without contagious diseases for a few days until the bacteriologic examination of the feces has been completed. It should be emphasized, however, that a careful history should be taken regarding previous admission of infants to hospitals. This information is of crucial importance in the case of an infant previously admitted to a ward with E.E.C. enteritis, since he may have become a carrier and thus the source of

an epidemic, as mentioned above. Every effort must be made to avoid cross infection.

Equally as important as the prevention of an epidemic is the early control of an institutional outbreak. General agreement has been reached regarding a plan to be followed under such a circumstance, as admirably discussed by Wheeler[82]: (1) New admissions to the contaminated ward must be discontinued. (2) All infants on the ward, both with and without diarrhea, should be given a suitable antibiotic, preferably neomycin. (3) Care must be taken that the attending staff does not transfer the infecting microorganism to other areas of the institution. Nurses, for example, should not have simultaneous responsibility for infants with E.E.C. enteritis and for children with other diseases. (4) The prevention of E.E.C. enteritis in nurseries depends in part upon avoidance of overcrowding, adequate nursing staff, terminal heating of formulas, use of individual equipment for each infant, adequate handwashing techniques, and the proper understanding of the principles of unit care, as well as the prompt reporting of cases. Useful information on the construction of nurseries for the care of infants with enteritis has been presented by Rogers.[64] The New York State Health Department has regulations in force to accomplish these ends. When the epidemic has been brought under control and the last infant has been discharged or transferred, the ward should be thoroughly disinfected. (5) All the measures devised for the control of infections in general must be strictly enforced. (6) A continued educational program regarding the prevention of cross infection must be undertaken.

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"Miss Rose S., a little girl, aged 5 years, had been troubled for about three months with a constant, though not profuse, discharge of slightly purulent mucus from the right nostril. . . . Not being able . . . to find anything wrong in the nasal passages, I looked to the condition of the teeth; and, finding the right upper canine carious, removed it. . . . The discharge . . ., in the course of a day or two, disappeared altogether.

"This short account may, perchance, afford a useful hint to some one; at any rate, it is a good illustration of reflected irritation, and teaches us that often times the *fons et ovigo mali* is not just where we might expect to find it."

Obstinate Chronic Discharge From the Nostril Removed by Extraction of a Carious Tooth, by Alfred Fleischmann, Associate of King's College. From the British Medical Journal, April 9, 1859.

Clinical Pathological Conference

The Children's Medical Center
Boston, Mass.

Sidney Farber, ***Editor***
John M. Craig, ***Assistant Editor***

THIS infant, one of twins, was admitted to The Children's Medical Center at 10 days of age because of intermittent cyanosis. She and her twin were the result of the second pregnancy of their 22-year-old mother. This pregnancy was complicated by mild hypertension. Labor began two weeks prematurely. At birth, the patient weighed 5 pounds, 2 ounces and her thriving twin sister weighed 4 pounds, 2 ounces. No description of the placenta or membranes was available.

Shortly after birth respiratory difficulty was noted and because of this and recurring attacks of cyanosis, she was kept in oxygen intermittently. The attacks were related to feedings rather than to crying. Her respiratory distress persisted even during periods without cyanosis. A roentgenographic examination on the sixth day of life revealed cardiomegaly, which increased over the next four days.

On admission here the baby was dyspneic and slightly cyanotic about the eyes. She was inactive but did not respond to stimuli. The vital signs were: temperature, 100° F., respirations, 60, and pulse, 150 per minute and irregular. The blood pressures by the flush method were 40 in the arms and 35 in the legs. A dry maculopapular rash with scattered pustules was present over the shoulders, upper trunk, and diaper area. The left chest was prominent and there was moderate inspiratory retraction of the sternum and the lower ribs. The heart was enlarged to percussion and a strong xyphoid impulse was both visible and palpable. The heart sounds were of poor quality and a gallop rhythm and soft scratchy systolic murmur were heard at the lower left sternal border. Apart from a few râles at the bases, the lungs were clear. The liver edge was felt 4.0 cm. below, and the spleen just below, the costal margins. No peripheral edema was present.

Laboratory data revealed: hemoglobin, 17 Gm. per cent, and leukocytes, 11,600 per cubic millimeter, with 40 per cent polymorphonuclear cells. A roentgenogram of the chest was interpreted as showing massive cardiac enlargement with relatively normal pulmonary vasculature. The electrocardiogram was interpreted as showing supraventricular tachycardia with

premature beats and abnormal ventricular conduction characteristic of Wolff-Parkinson-White syndrome; axis was 150. While evaluation of the hypertrophy was difficult, right ventricular hypertrophy was suspected. There were ST and T wave changes which may have been secondary to abnormal ventricular conduction but were so marked that myocardial or pericardial disease seemed quite likely.

The patient was placed in oxygen, and digitalis was given. The pulse became more irregular but the patient appeared to improve clinically. Eleven hours after admission the heart rate dropped to 50 per minute, the respirations became slow and irregular, and despite resuscitative measures, the infant died 15 minutes later.

DISCUSSION

DR. WILLIAM D. WINTER, JR.*—It would be nice to know a great deal more about this "maculopapular rash with pustles." Are the pustles the end stage of the maculopapular lesions? It is difficult to tell from the description if this was previously an impetiginous lesion or whether it was a miliarial lesion which will have some maculopapular elements. The patient is a little young for miliaria, since that lesion begins usually in the second to third week of life. Could the rash be related to a candida infection which may occur first about the anus? That would appear doubtful since this dermal lesion usually appears as a diffuse erythema with a raised edge under the diaper, from which maculopapular lesions spread up the trunk, but pustules are not seen. Could this be a diffuse herpetic lesion? These lesions appear first as a macule, quickly become vesicular, and then pustular, but since the pustular lesions appear sparse compared to the papules, this would seem unlikely. Smears and scrapings of such lesions would be helpful to demonstrate candida, staphylococcus, or the multinucleate giant cells of herpes. I am afraid the rash must be left as an ill-defined one.

The chief complaints of respiratory distress and cyanosis require the consideration of the possible difficulties in the central nervous system, lung, or heart. Since the patient has no other evidence of central nervous system disease, this can be eliminated. The duration of the disease rules out the hyaline membrane syndrome. We have no evidence of pneumonia so I believe we can eliminate the lungs as a cause of difficulty.

All the later data indicate that cardiac failure is the cause of the rapid respiratory rate in this child, but whether this is the most severely affected organ in a generalized disease or whether this is a primary disease of the heart remains to be seen.

The electrocardiographic findings of a conduction defect, a rhythm disorder, and the absence of a significant murmur indicate a myocardial disease rather than a congenital malformation. Could this infant's difficulty be a purely functional rhythm disorder, that of paroxysmal tachycardia? The cardiographic tracings are, in a sense, consistent with the Wolff-Parkinson-White syndrome, a descriptive term for an ectopic impulse with a short P-R interval and an irregular and protracted spread through the ventricular system, often associated with a tachycardia. The rate never went above 150, however, and it is hard to believe she would go into heart failure from

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this rate alone; or, again, would the gradual slowing of the rate and terminal abrupt onset of bradycardia as a result of digitalis therapy be consistent with this disorder.

There are many features that suggest a primary myocardial disease. These include: the low blood pressure, weak heart sounds, gallop rhythm, enlargement of the heart without chamber predominance, an arrhythmia associated with conduction abnormalities, and the downhill course in the absence of any known malformation. Cardiac glycogen storage disease, as an example of a myocardial disease which should have a later onset than this, is associated with ST and T wave changes but also has a more clear-cut left ventricular predominance. An aberrantly originating left coronary artery may give rise to an electrical record like this, but only after a month or two of life. The specific inflammations such as Fiedler's myocarditis, too, often have a later onset. Toxoplasmosis may cause a myocarditis with heart failure as well as an enlarged liver and spleen, but in a newborn infant one would expect to have evidence of central nervous system involvement; a rash might be seen but not of a pustular type. Herpes, although it may be a generalized infection, does not ordinarily give rise to myocarditis. The same may be said for cytomegalic inclusion disease.

An infection with Coxsackie virus in a newborn infant may give a clinical appearance entirely consistent with this one. The chief symptoms are dyspnea, tachycardia, fever, and those of central nervous system disease, the latter two of which this infant did not have; the chief physical signs include cyanosis and enlargement of the heart, liver, and spleen. Myocarditis and pericardial effusion are common findings. The greatly enlarged heart, by roentgenographic examination, here may be due to a combination of chamber enlargement and pericardial effusion, while the queer murmur may be related to pericarditis.

The pyogenic infections such as those due to staphylococcus, salmonella, or candida may give quite similar manifestations in a newborn infant, but one would expect more evidence of widespread sepsis, as stupor, depression, jaundice, pneumonia, and a high leukocyte count; particularly if pericarditis is associated, there should be a pneumonic process.

Endocardial fibroelastosis is another condition affecting the myocardium in early life, with many features in common with the infant under discussion, but left ventricular hypertrophy and pulmonary congestion are also usually present. Such infants do not have weak heart sounds, gallop rhythm, or gross conduction disturbances unless there is a terminal myocardial necrosis in the last weeks of life.

Primary tumors of the heart, such as rhabdomyosarcoma, with infiltration of the ventricular wall will give electrocardiographic evidence of vascular impairment and myocardial anoxia. These infants may have a pericardial effusion from necrosis of the superficial part of the tumor and have a poorly responding, greatly enlarged heart, with death resulting in the first weeks of life. However, there is nothing in the protocol to distinguish such a lesion from a Coxsackie infection.

Could the fact that this infant was a twin have any bearing on her fatal disease? Two thirds of all twin pairs, whether mono- or dizygous, are of the same sex. Of these two thirds, one fourth are monozygous, so in three of eight chances these infants would have

been monozygous twins. In some monozygous pairs anastomoses exist in the placenta between the umbilical vein of one infant and the umbilical artery of the other; this allows a gradual transfer of blood from one infant to the other to its detriment, being heavier, having an enlarged heart, and, in many instances, evidencing cardiac failure at birth or shortly thereafter. The time element makes this problem unlikely in this infant, for she lived for two weeks. The sibling donor twin will be small an anemic, having difficulty in initiation of urinary function due to the presence of inspissated material in the kidneys.

Is it possible to have an infection serious enough to cause death with myocarditis in one of twins without injuring the other? There has been one reported case of fatal toxoplasmosis in one twin in which the other twin had only a minor chorioretinitis. I do not know whether this can occur with Coxsackie infection, but I do not think infection can be ruled out because of the failure of involvement of one twin.

I cannot say which one of the several diagnoses is the right one, but I believe a Coxsackie infection is the most likely, second, a tumor, and third, endocardial fibroelastosis with more than the usual amount of myocardial necrosis to account for death.

DR. FARBER.—Thank you, Dr. Winter. Were there any x-rays, Dr. Neuhauser?

DR. NEUHAUSER.—None were made here, but through the kindness of the Providence Hospital in Providence, Rhode Island, we have some of their films. On the lateral film the heart is filling up a considerable portion of the chest and is certainly big enough to account for the prominence of the thoracic wall anteriorly. I do not see any aerated lung. On the anteroposterior film the liver is a little large. There is no evidence of splenic enlargement. We have this enormous heart which is globular and melon shaped; it approaches and touches the left chest wall (Fig. 1). It would be hard, from these data, to determine which chambers are enlarged, if any, or whether this is an over-all diffuse

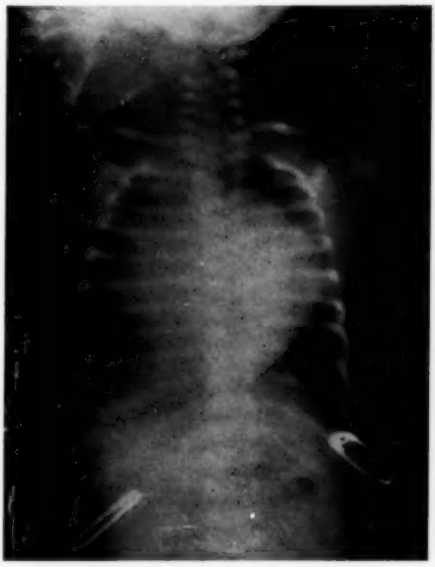

Fig. 1.—Roentgenogram of chest. The heart shadow is greatly enlarged bilaterally.

enlargement. It is always very important to determine, if possible, the state of the pulmonary vasculature; the protocol says it was essentially normal and I think that is probably true. When we are confronted with a very large heart early in infancy, we immediately wish to know if the pulmonary vessels are increased in prominence. Then, we begin to consider congenital malformations such as transposition of the great vessels. If they

are diminished in prominence, we begin to consider severe pulmonary stenosis or Ebstein's malformation. If they are normal, the first thing to be excluded is a coarctation of the aorta; having done that, next consideration is the group of primary myocardial diseases that Dr. Winter has discussed so thoroughly. From the film alone, I think the myocardial group of disorders, rather than the congenital malformations, might be discussed.

DR. FARBER.—The protocal gives only one interpretation of the electrocardiographic findings. Dr. Braudo, would you give us the detailed report?

DR. MICHAEL BRAUDO.—The rate was 150 per minute, the P-R interval, 0.05 second, the QRS, 0.10, and the QT interval, 0.28. In the standard limb leads a high nodal or ectopic auricular tachycardia with fairly frequent supraventricular ectopic beats was present. There was a prolonged ventricular depolarization period. The T wave in Lead I was inverted, with marked elevation of the ST segment. In Lead III there was a depressed ST segment and inverted T. In the unipolar limb leads in aV_R, the R wave was 22 mm., with marked depression of the ST segment; the ventricular activation time was 0.07 second. In the semipolar trunk leads there was complete RS reversal from V_{4R} to V_8. In V_1 the R wave was 13 mm.

DR. FARBER.—Dr. Liebman, would you care to comment on these findings?

DR. JEROME LIEBMAN.—I would like to emphasize that the marked intraventricular conduction defect with a very wide QRS complex but without a short PR interval is not just like the symptoms in Wolff-Parkinson-White syndrome. All the ST and T wave changes, which were very severe, could be explained on the basis of marked widening of the QRS complex that is secondary to the intraventricular conduction defect. The tall R waves in the left chest and in the right chest which ordinarily imply hypertrophy also could have been due to the marked intraventricular conduction defect. Thus, we do not know with certainty whether they really were primary ST and T wave changes or whether they could have been explained by the intraventricular conduction defect which was certainly the most prominent part of the picture. This is an almost unique picture. These changes are not solely due to the tachycardia.

DR. CRAIG.—May I ask, how often do you get, in endocardial sclerosis, irregularity in atrioventricular conduction? I understand that ventricular tachycardia is not uncommon.

DR. LIEBMAN.—That is so only in association with failure. The marked change here was not in the atrioventricular conduction pattern but in the ventricular.

DR. CRAIG.—And what of the premature auricular beats?

DR. LIEBMAN.—They are merely evidence of cardiac failure.

DR. FARBER.—You say this is unique, but you have encountered other cases with ventricular conduction defects, have you not?

DR. LIEBMAN.—Yes.

DR. FARBER.—What are the usual causes?

DR. LIEBMAN.—Well, most of those that we have seen have either been patients with the Wolff-Parkinson-

White syndrome, or patients with various congenital heart lesions such as congenital heart block, and also various other congenital heart lesions shortly before death. No one knows exactly what causes the Wolff-Parkinson-White syndrome, the theory is that there is an abnormal conduction pathway bypassing the regular atrioventricular conduction pathway in the so-called bundle of Kent, which is shorter than the regular atrioventricular conduction pathway. This gives a short PR interval and a long QRS complex.

DR. FARBER.—What were the clinical diagnoses?

DR. BRAUDO.—The diagnosis was not really known. The cardiologist who saw the patient did not commit himself. The opinion was that this represented a case of primary myocardial disease, probably endocardial fibroelastosis.

DR. NEUHAUSER.—Have we ever seen a heart this large caused by fibroelastosis at this early age?

DR. CRAIG.—It was bigger than any I have seen.

DR. FARBER.—I am very much interested in the interpretation of the electrocardiogram. There was a paper written about thirty years ago which predicted that this kind of finding would be made if electrocardiograms were taken with regularity on infants.[2] We will make further reference to that paper a little later. Who would hazard a guess, if not a diagnosis?

DR. JANEWAY.—I recollect, Dr. Farber, the largest hearts described in early infancy have been associated with aberrant coronary arteries.

DR. FARBER.—Yes, that is so. In glycogen storage disease the heart can be very large also. One extremely large heart, I recall, proved to be liver coming up into the pericardial sac through a diaphragmatic hernia, and I think it was Dr. Gross who proved that it was liver at operation and not heart.

DR. NEUHAUSER.—A small tumor of the heart may, with fluid effusion, give a shadow of this kind. Also, a teratoma of the mediastinum may give a very large heart shadow.

Fig. 2.—The right heart chamber, opened. At the arrow is the tumorous involvement of the heart valve.

DR. CRAIG.—This child had, I think, the biggest heart for this age that I have ever seen, and it was larger than the sum of the lungs in size. It was quite well proportioned and on the external surface no real inequality of the surface was noted.

When we opened the right atrium, the tricuspid valve was seen to contain a huge tumor mass which narrowed the orifice of the tricuspid valve very markedly. The right ventricular chamber occupied only a very small portion of the total mass of the right side of the heart because of a bulging of the

interventricular septum. The tumor mass extended down along the moderator band, and there was some thickening of the endocardium. The mitral valve was also practically occluded by a large tumor mass. The left ventricular chamber occupied a very minute portion of the total mass of the heart and was a little appendage on the side of this huge interventricular septal mass. The foramen ovale was open. On cross section the huge tumor mass occupied the entire interventricular septum and extended upward to involve both atrioventricular valves. There were also gross and microscopic evidences of some necrosis of the normal muscle as well as necrosis of the tumor. The coronary vessels had a normal distribution except in the region of the intraventricular septum where the vasculature was insufficient in comparison to the right ventricle and the left ventricular portions. There was some endocardial sclerosis in the right and left ventricle.

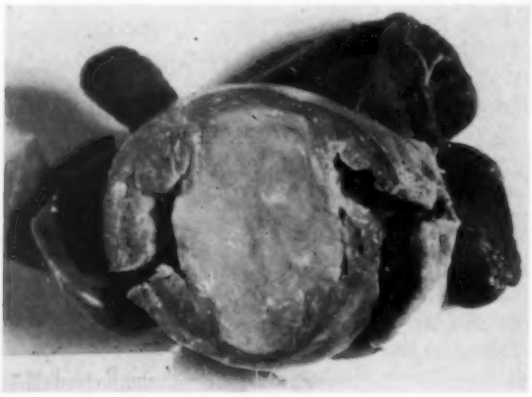

Fig. 3.—The heart has been sectioned coronally; the interventricular septum has been replaced by a gelatinous tumor.

The major lesion, a so-called *Rhabdomyoma* with many small independent areas of rhabdomyomatous malformation, was composed of the typical spider cells with central nuclei. Some of the cells were more immature, and several radiating strands contained cross striations. Such malformations are, of course, commonly associated with tuberous sclerosis or phacomotosis, which is a familial hereditary syndrome associated with tumorous malformations of the brain, liver, and kidney and with adenoma sebaceum in older children. In the lower pole of the right kidney there was a small area of cyst formation seen grossly and a focal microscopic area of cystic malformation of the kidney. These may be part of the constellation of malformation seen in tuberous sclerosis. The brain did not show any abnormalities, either microscopically or grossly. It had a uniform density as one passed one's hand over it; there were not the usual bumps and hard areas in it which one usually finds in cases of tuberous sclerosis. There are at least 73 rhabdomyomas of the heart reported in the literature and of those,

in the first 2 or 3 months of life almost none of them had cerebral changes that were recognized. This may be due partly to the fact that the brains were not carefully examined, although in this case no lesions appeared in the brain. We have had other cases in which there have been isolated rhabdomyomas, again without changes in the brain; the majority, if they live more than a few years, have extensive changes of tuberous sclerosis of the brain. It will be interesting to know what the status of the sibling was at this time. She undoubtedly will have to be watched very closely for development of changes of tuberous sclerosis because this has a dominant hereditary pattern.

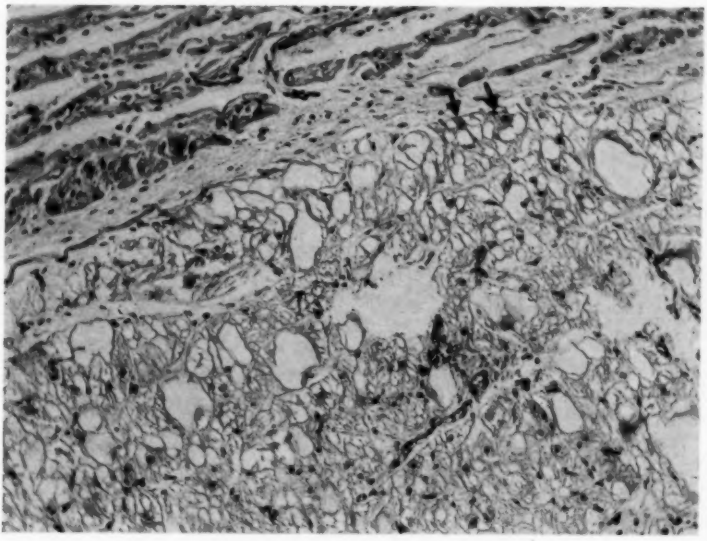

Fig. 4.—Photomicrograph of the heart. At the junction of normal and abnormal muscle are "spider cells" (at arrow). (Hematoxylin and eosin ×185.)

DR. FARBER.—Thank you, Dr. Craig. I think the impression, from the literature and from studies we did years ago, is that the two processes could be quite independent of one another. Those who die early may have large tumors of the heart, while those who live have smaller cardiac tumors and have involvement of the brain. Most of the patients reported are from institutions for mentally defective or retarded children. Dr. Byers, do you have any information on this?

DR. RANDOLPH BYERS.—The children who have tuberous sclerosis and who develop the so-called Pringle's disease of the face show no skin lesions that are grossly discernible in early life, but as they get to be 3 or 4 or 5 years of age, most of them develop them. I can remember one child whose mother said that as a baby he had speckles on his cheeks. However, I have inquired very carefully from several families and I have seen two or three second children myself in whom

as young infants you could see nothing in the skin, but the lesions were quite obvious at 4 or 5 years of age.

DR. FARBER.—This is the so-called adenoma sebaceum?

DR. BYERS.—Yes. This, of course, is related to the same disease. Now the brain lesions might do the same sort of thing. I know of only one child who has had two pneumoencephalograms, one of which was fairly normal; the other one showed the so-called candle gutterings on the inside of the ventricles 4 or 5 or 6 years later.

DR. FARBER.—A number of students of the subject, years ago, thought that these cells forming the heart tumors arose from the Purkinje cells; they predicted that there would be EKG changes if they were sought for. This was in the days before electrocardiography was commonly used in pediatrics. This is the first example, Dr. Craig, that I can recall with such striking electrocardiographic changes.

DR. CRAIG.—I think this case is one of the few in which a cardiac tumor has been clinically manifest. There is one case of auricular extrasystoles with partial atrioventricular block which was described about 4 or 5 years ago, and as far as I can tell, in a fairly rough review of the literature, these are the only two cases in which there has been actual clinical difficulty as a result of rhabdomyomas, which are usually found at autopsy. They may be so small as to be seen in an isolated section, microscopic in size.

DR. FARBER.—I am very much interested that you brought up the subject of twinning because this recalls the theory of Steinbiss.[2] He believed that in such cases there may be a surplus formation of parts which would give rise to such tumors in tuberous sclerosis, with excess formation of tissue in the heart, kidney, and brain, this excess tissue being composed of embryonic stages of the normal elements. I cannot recall any evidence from the literature that twinning was of any importance in other cases of tuberous sclerosis.

DR. NEUHAUSER.—What did the skin lesions prove to be, Dr. Craig?

DR. CRAIG.—Unfortunately, in all the skin sections we have, no lesions were present.

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Comments on Current Literature

CHROMOSOMAL PATTERNS IN MAN

THE issue of *Nature* for November 10, 1956, carried a summary article by Ford and Hamerton[1] entitled "The Chromosomes of Man." These authors pointed out that in all probability human genetics was first emphasized in 1891 by Hansemann[2] and that this publication would appear to be the first record of attempted chromosomal counts in human cells. Within the two decades following diploid numbers ranging from 16 to 36 were reported, until 1921, when Painter's[3] classic work gave the diploid number of chromosomes in man as 48 in both sexes: 23 pairs of somatic chromosomes or autosomes and 2 sex chromosomes designated as X and Y in the male; 23 pairs of autosomes, plus XX in the female. This total number of 48 chromosomes was accepted for many years. However, in 1956, Tjio and Levan[4] were able to make consistent and verifiable counts in cultures of lung tissue taken from several aborted embryos and concluded that the diploid number in man is 46. Within the past three years information has been accumulating, and it is now generally accepted that 46 (diploid) is the correct chromosome number for man. The count of 48 chromosomes may have been due to technical difficulties leading to artifacts; certainly the technical advances in histologic and cytologic methods have been many since the initial work of Painter in 1921 to 1923. Ford and Hamerton[1] state that the erroneous counts can be explained also on the basis that there is a tendency for the individual chromosomes of man to develop constrictions, which could lead easily to misinterpretation concerning the relationship of the chromatin masses to each other. Spermatocyte counts of 24 could have arisen as a consequence of precocious disjunction of the sex-chromosome pair, X and Y; early separation of the paired sex chromosomes, as compared with autosomal pairs, has been observed in various species. More important, however, are the improved techniques now employed in the study of chromosomal patterns. The newer methods, which have been aimed at separation and gentle dispersal of the chromosomes, involve the use of hypotonic solutions to bring about swelling of the chromosomes and the so-called "squash technique" to separate them in a manner more conducive to accurate counting. These more recent counts have led to the conclusion that the chromosomal complex of man consists of 44 somatic chromosomes, plus X and Y in the male, 44 somatic, plus XX in the female, bringing the normal diploid total to 46.

With the development of these improved cytologic methods, considerable interest has been aroused among clinicians in the study of human genetics, more particularly in the present instance with reference to chromosomal patterns. Interesting reports have appeared recently which contribute to a better understanding of certain clinical syndromes. Many of these constitute baffling medical conditions in the absence of this definite genetic explanation. In the January 31, 1959, issue of *Nature* Jacobs and Strong[5] report a case of human intersexuality having a possible XXY sex-determining mechanism. The case described is that of an

apparent male, 24 years of age, with gonadal dysgenesis, gynecomastia and small testes, associated with poor facial hair growth and a high-pitched voice. Microscopic examination of the seminiferous tubules revealed hyalinization and atrophy. Cells from the buccal mucous membrane, studied by the method of Barr and Bertram[6] for the identification of "nuclear sex chromatin," indicated that this chromatin pattern was that of the female. From a study of blood cells and of cultured cells from sternal bone-marrow material, the patient's sex-chromosomal pattern was established as XXY in type. Similar bone marrow studies carried out on tissue from the parents of this patient revealed normal chromosomal pattern and number in both parents. The authors suggest that the extra chromosome might be accounted for on the basis of "non-disjunction at either mitosis or meiosis during gametogenesis in one or other parent."[5] An alternate explanation, according to the authors, is the possible occurrence of nondisjunction during the patient's very early embryonic development, in which case this patient might correspond to the sex-mosaic type observed in certain of the lower animals.

With some of these biological counterparts in mind, studies of mongoloid patients have been carried out. Reports within the past few years indicate that in this condition there are 47 chromosomes and that the mongoloid individual has an extra single chromosome, the additional one being a small somatic chromosome (autosome).[7] A very interesting report was published by Ford and his associates[8] in *Lancet* for April 4, 1959; a case of Klinefelter's syndrome and mongolism in the same patient is described. This patient, an imbecile 45 years of age, showed manifestations typical of Klinefelter's syndrome and of mongolism. Microscopic study of skin cells and cells from the buccal mucosa showed the presence of the Barr chromatin body, identifying the type as potentially female. Clinically, the patient had small testes, scanty facial axillary and pubic hair, slight gynecomastia, and feminine distribution of fat. The testes were atrophied and no spermatogenesis could be detected. The mongoloid traits were those considered characteristic of this condition. Bone marrow material, cultured in tissue culture, was studied intensively and repeated chromosome counts of 48 chromosomes were obtained. The authors concluded that this patient has 48 chromosomes with the following distribution: 23 normal pairs, one of which is the XX pair as in the female, and in addition a Y chromosome and an extra small somatic chromosome. A normal pair of these small somatic chromosomes was present in the chromosomal configuration of 46, so that this particular individual shows the additional small autosome typical of mongolism and the extra sex chromosome, the Y, typical of the Klinefelter syndrome.

In a separate publication appearing in the same issue of *Lancet*, Ford, Jones and their associates[9] report the chromosome findings in a case of gonadal dysgenesis (Turner's syndrome). The patient was seen first at 14 years of age because of primary amenorrhea and absence of secondary sexual characteristics; she was short of stature and retarded in school progress for her age level. Failure of the normal secondary sex characteristics of puberty and the rudimentary state or possible absence of the gonads fulfilled the clinical description of Turner's syndrome. Studies of smears from the buccal mucosa prepared according to the Barr-Bertram method revealed that this patient was negative for the nuclear chromatin body which is characteristic of the female. Bone-marrow cell studies indicated a chromosome number of 45, rather than 46. The sex chromosome pattern was identified as XO, since one X chromosome was lacking completely in all the counts made. In an attempt to explain this abnormal chromosome pattern the authors refer to counterparts reported in some of the lower animals which are well verified. If in the process of oögenesis (at meiosis), the members of the X-chromosome pair fail to separate from each other

and both pass to the polar body, the result would be a mature gamete which carries the normal haploid number of autosomes but lacks the X chromosome (22 haploid number). If such an ovum is fertilized by a spermatozoan bearing the X chromosome (23 haploid), the potential new individual (zygote) would receive the normal diploid component of autosomes but would have only one X-chromosome (diploid number, 45). In lower forms such as the fruit fly, Drosophila, this individual is the recognized XO type and is a sterile male. The authors' findings in the case reported suggest that in man an XO zygote develops into a sterile agonadal individual whose body type is female.

In analyzing published reports and their own findings these several authors present some interesting speculations. One group particularly is interested in the possible correlation between mongolism and a predisposition to the development of leukemia.[7] The possible association between mongolism and leukemia has been discussed in the medical literature for about three years, and the presence of an abnormal chromosome number has been reported in at least one case of acute human leukemia.[10] This predisposition to leukemia in a group of individuals with some abnormality in karyotype may be of real importance. Closely related to this problem are some of the mechanisms of carcinogenesis which might be associated with changes in genetic patterns.[11] Certain human carcinoma cells studied and established in tissue culture show abnormal mitotic figures and abnormal chromosome numbers.[12] Another interesting discussion concerns the report that a significant percentage of male mentally defective patients garnered from various institutions was found to have an abnormal karyotype pattern, the XXY chromosome configuration in anatomically male patients. With the current increased interest in human genetics and the remarkable technical improvements developed recently in cytogenetics, it seems possible that some of the mysteries surrounding constitutional predisposition to illness and the subsequent development of clinical syndromes may be elucidated by a study of the chromosomal patterns in these patients.

RUSSELL J. BLATTNER

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The Jenner statue by W. Calder Marshall, R.A., erected in 1858 by popular subscriptions from many countries, was first placed in Trafalgar Square, London. Later, in 1862, it was moved to Kensington Gardens. (Photograph Crown Copyright. Reproduced by permission of the British Ministry of Works.)

THE STATUE TO JENNER

A CENTURY after his birth in 1749, a movement was started in England to raise funds by popular subscription for the erection of a statue honoring William Jenner, the originator in 1796 of vaccination against smallpox. That Jenner was deserving of such an honor was recognized by physicians in all parts of the world, as evidenced by their contributions to the fund. We know of no other physician who developed a therapeutic measure which today, over a century and a half later, is used routinely by physicians in every part of the world.

Recently, while browsing through the pages of the *British Medical Journal* for 1858, I encountered an interesting description of the controversy that arose in regard to the erection of the statue in Trafalgar Square in London. The first reference was a quotation from the *Times* in the issue of May 8, 1858 (p. 375) under the heading "This Week."

> Now that the statue of Jenner is on the eve of being inaugurated, the *Times* raises an objection against placing it in Trafalgar Square, on the ground of "inappropriate location." The "Thunderer" thinks Lord John Manners very ill advised to place the hero of vaccination by the side of the hero of Scinde, and with the prospect of Havelock as a companion!
>
> "Why should Dr. Jenner be found in such formidable society? We need scarcely say that we consider such men as Harvey, Hunter, and Jenner, to be quite as worthy to be held in public honour as any warrior who ever lived, but we would not see them placed in ridiculous juxtaposition with men whose careers and merits were entirely different than their own. . . . The expense of removing this unfortunate statue of Dr. Jenner to some more suitable position can be but very trifling, and we earnestly trust that the public authorities will not insult the commonest feelings of taste and propriety by leaving it where it is now placed."

To this the Editor comments:

> It would be a very ill advised act on the part of Lord John Manners, or any one else, to remove the statue of Jenner from its post of honour among heroes; and we trust, in the name of national gratitude and common sense, that no more nonsense will be uttered against giving one of the greatest benefactors of mankind that place, which is of right his, among those who have deserved well of their country.

In the following week's issue there appears some of the discussion that took place in Parliament on the subject along with the contribution of the Journal's Editor to the controversy.

> "Parliamentary Proceedings"
>
> Lord A. Vane-Tempest said that an erection had lately grown up in Trafalgar Square, which had not yet been uncovered, but on inquiry he was informed that it was a statue of Dr. Jenner. He had no desire to depreciate the profession of which Dr. Jenner was an ornament, but he submitted that the site in question was not an eligible one for a statue to Dr. Jenner. He wished to ask the Chief Commissioner of Works whether the selection of the site was his or that of his predecessor in office;

and if there was any correspondence on the subject, or whether it had been referred to any committee of taste? He should like to be told who generated Dr. Jenner in that place. (A laugh)

Lord Elcho said . . . he wished to know if the government had any fixed principles on the subject—that is, whether if any set of gentlemen subscribed for a statue, they could select a site for it. The statue of Jenner was placed in a line with that of Sir Charles Napier. He wanted to know if the line was to be completed, and if there was to be a line of statues along Trafalgar Square; and also whether it was to be a single line or a double line. The English formation was two deep, and the French formation three deep. Which formation was to be adopted in Trafalgar Square, the French or the English? There ought to be some principle on which statues were to be erected, so that they would not be a disfigurement to the metropolis.

Mr. T. Duncombe . . . Cowpox was a very good thing in its proper place; but it had no business among the naval and military heroes of the country. Everybody spoke with ridicule and disgust of the statue; and if the Government should not feel justified in stopping the work, he trusted that the House would pass a resolution calling on them not to pollute and desecrate the ground by erecting a statue there to that promulgator of cowpox throughout the country. . . .

These remarks obviously aroused the ire of the Editor, as evidenced by his editorial, "Where Shall We Place the Statue?"

We wonder what the foreign subscribers to the Jenner Testimonial will think of the questions raised in Parliament with reference to the placing of the discoverer of vaccination in Trafalgar Square. Will they not open their eyes with wonder and astonishment, at the spectacle of member after member of the House of Commons getting up and demanding the expulsion of the effigy of one of the most illustrious of Englishmen, and one of the greatest benefactors of mankind, from the place of honour in which it is already located? Will they not sneer at the civilisation of these islanders, who think the statue of a Napier is polluted by such company—who so scornfully imply that the hero who triumphed over a loathsome disease is not worthy to sit at the feet of the hero of Scinde? Lord A. Vane-Tempest, who so condescendingly stated in the House on Friday last week, that "it was not his intention to say anything in depreciation of the profession of which Dr. Jenner was so great an ornament," gave it as his opinion "that the site selected was an ineligible one." This is pretty well for a young lording, who would perhaps not object to have the site appropriated to a statue some day to the illustrious memory of that distinguished knight and soldier, the Honourable Charles Beaumont Phipps, so ludicrously bracketed with Havelock; but it is in simple modesty to the ravings on the same subject of Mr. Thomas Duncombe. "Cowpox," said the member for Finsbury, was a very good thing in its place, but it had no business among the naval and military heroes of the country. . . .

Lord John Manners will, we trust, shut his ears to the voices of those who wish to prove that Trafalgar Square is too good a site for such a man. We see no reason whatever that the finest site in Europe should be appropriated to the effigies of soldiers only. Why should those who destroy be ever placed in the front rank, whilst the philanthropist and the philosopher are only permitted to occupy out-of-the-way corners in forgotten squares, from which the living tide of man has long since ebbed? We are told that Lincoln's Inn Fields would satisfy the claims of Jenner; but if the publicity of the situation of an effigy should be measured by the universality of the benefit the original has conferred on mankind, we say emphatically that no statue that is or can be placed in Trafalgar Square could for one minute compare with that of the illustrious discoverer of vaccination. The House of Commons should remember that this statue is no Stoke Pogis glorification of some great unknown—it is the offering to British pride of every civilised nation. The subscriptions from all parts of the world have been most munificent, and we should indeed be committing an act of national indecency and discourtesy if we were to deny a worthy site for so generous

an offering. According to Sir John Herschel, London is the center of the terrestrial globe, and Trafalgar Square is the center of London. Here, and here only, then, should we raise the statue of a man whose labours have already borne fruit far beyond the limits of civilisation, and must in the end confer their infinite benefits upon the whole human race.

The opposition to the erection of the statue in Trafalgar Square seemingly lost out, as the next issue of the Journal (May 22, p. 421) contains a report of "The Inauguration of the Jenner Statue."

On Monday last, at 3 P.M., the statue of Dr. Jenner was inaugurated by His Royal Highness the Prince Consort, at the College of Physicians, Pall Mall East.

His Royal Highness said, that he attended there to do honour, with those present, to the memory of Jenner, that being the anniversary of Jenner's birth, and in order to mark his sense of the inestimable benefits bestowed upon the human race by that great philosopher and philanthropist. (Applause.)

Although it is believed that attempts were made on more than one occasion to carry out the idea of a metropolitan monument to the discoverer of vaccination, nothing practically effective was done previous to the autumn of 1850, when a number of gentlemen having learned that Mr. Calder Marshall, R.A., had designed a statue of Dr. Jenner, arranged a meeting, at which a resolution was passed . . . if it were executed in bronze and placed in a proper situation in the metropolis, it would form an appropriate monument and in accordance with this, a preliminary committee, with a view of raising subscriptions for this purpose, was immediately formed.

As the benefit of Dr. Jenner's discovery is not limited to British subjects, but has extended to the whole civilised world, the committee are of opinion that the subscriptions should not be exclusively confined to his compatriots. . . .

This appeal was responded to in a manner which exceeded the most sanguine hopes of the committee, and it soon numbered in its ranks eminent men from every country of the world, anxious and eager to do honour to the memory of Jenner. . . . America, with her usual energy, early took the lead, and, chiefly through the zealous activities of Drs. Jackson, Ware, and Warren of Boston, and those of Drs. Dunglison, Mütter, and Wood of Philadelphia speedily transmitted subscriptions to a large amount. Russia also came forward in the most liberal manner. . . . They had transmitted *the first installment* before the outbreak of the late war [Crimean War, 1853 to 1856]. During its continuance, all intercourse was, of course, suspended. No sooner, however, was it renewed, on the return of peace, than they hastened to forward the balances, which they had kept through all the asperities of the contest, as a deposit sacred to the great cause of humanity. Several contributions were also received from Professors Retzius, of Stockholm; Holst, of Christiana; and Schroeder van der Kolk, of Utrecht, as representing the committees of their respective countries; and last, not least, from Professor Buniva and the sub-committee at Turin; the subscription in Sardinia being, perhaps, larger in proportion to its population than that of any other country.

The statue has, by the permission of Her Most Gracious Majesty, been erected on a most eligible site, in Trafalgar Square, and is now placed under the care and guardianship of the British Government.

This seemingly ended the matter. Curious, however, as my attention had never been drawn to the statue during a number of visits to London over the past fifty years, I queried one of my London friends and colleagues if the Jenner statue still stands in Trafalgar Square. He in turn queried the Royal College of Physicians, still located on Pall Mall. The reply by Mr. L. M. Payne, Assistant Librarian to the College, was sent me: ". . . the Jenner statue by W. Calder Marshall, R.A., now stands in Kensington Gardens. . . .

Kent's *Encyclopedia of London,* and Sir D'Arcy Powers' *British Masters of Medicine,* both state that it was erected in Trafalgar Square in 1858 and removed to Kensington Gardens in 1862."

This surprising development of the story led to a search through the *British Medical Journal,* 1859 to 1862, to find what the Editor would have to say about the removal in light of the discussion reported above. Finally, a brief note was found in the issue for February 15, 1862, entitled "Removal of the Statue of Dr. Jenner."

> During the last few days the public have been surprised, on visiting Kensington Gardens, to find the statue of Dr. Jenner of small-pox-vaccination celebrity, standing, or rather sitting down, with its usual air of placidity, on a brand new pedestal in Kensington Gardens, in the vicinity of the stone bridge spanning the Serpentine, on the Bayswater side. The statue, it will be remembered, was some time ago promoted to a distinguished place near the Nelson Column in Trafalgar Square; but it has been suddenly removed to its present position in Hyde Park.

This was all. No further information could be found in any of the available books and articles on Jenner. Subsequently, Mr. Payne informed me in a note that *Lancet* of that same date, February 15, 1862, also contained a note in a similar vein. However, it throws no further light on the events leading up to the removal of the statue to the new site. With its removal *fait accompli,* the Editor and Journal apparently gave up the fight. It would be interesting to know what led up to its removal. Was there perhaps an organization such as the G. A. R. of our youth or the American Legion of today which brought political pressure on the government to keep Trafalgar Square sacrosanct for military heroes? The answer probably lies buried in the records of the Commissioner of Works between the years 1859 and 1862, if they still exist. One thing is certain: The work of Jenner will be a living influence in years to come, when the name of Lord Nelson is but a dim figure of historic interest.

Perhaps, after all, it is far more fitting that the statue of Jenner found its permanent home in Kensington Gardens rather than among the warrior heroes of the British Commonwealth. In Trafalgar Square, Lord Nelson, with his back to British art and culture as he gazes down Whitehall toward Parliament, is so loftily perched on his column that he looks out beyond the pigeons that infest and dirty the Square, the sight-seeing tourists, and the occasional mobs of "-ists" of one breed or another who use the Square for demonstrations. Jenner from his lower pedestal would have had to contemplate these rather uninspiring sights for a century. In Kensington Gardens, immortalized to English-speaking peoples by the gentle and whimsical Sir James Barrie, we can think of Jenner looking down benignly on the many generations of children who have found health and happiness playing in the Gardens, and perhaps thinking to himself, "It was due to me that many of these children are alive today." Perhaps he has been much happier in these surroundings.

Borden S. Veeder.

I wish to express my thanks to Dr. Kenneth Tallerman of London for his help in tracing the story of the statue and for obtaining the photograph.

News and Notes

At the May meeting of the **Society for Pediatric Research**, the following officers were elected:

President: Dr. Henry Barnett

Vice-President: Dr. Frederic N. Silverman

Secretary-Treasurer: Dr. Clark D. West

To Council: Dr. Edna Sobel, Dr. Forrest H. Adams, Dr. Irving Schulman, Dr. Alfred Bongiovanni, Dr. Wallace McCrory, Dr. Robert Slater

The following were elected to membership:

Moises Behar, Vanderbilt

Robert M. Blizzard, Ohio State

Robert E. Carter, Chicago

William A. Cochrane, Dalhousie, Halifax, N. S.

Marion E. Erlandson, Cornell

Francis X. Fellers, Harvard

Park S. Gerald, Harvard

Thomas A. Good, Maryland

Douglas C. Heiner, Arkansas

Doris A. Howell, Duke

L. Stanley James, Columbia

William Krivit, Minnesota

Earle L. Lipton, New York State at Syracuse

J. F. Lucey, Vermont

A. James McAdams, Children's Hospital at Oakland

Donald M. McLean, Toronto

Arthur E. McElfresh, Temple

George M. Maxwell, Wisconsin

Edward A. Mortimer, Jr., Western Reserve

H. David Mosier, California at Los Angeles

William A. Newton, Jr., Ohio State

William L. Nyhan, Johns Hopkins

Thomas H. Shepard II, Washington

M. Michael Sigel, Miami

Katherine Sprunt, Columbia

Robert S. Stempfel, Jr., Duke

Daniel Stowens, Southern California

Bernard M. Wagner, Washington

The **Second Annual Symposium of the Memorial Hospital** on *New Horizons in Medicine* will be held Dec. 2, 1959, in the new Memorial Hospital of Long Beach in conjunction with the formal opening of the 400-bed hospital. For further information, write to Dr. George X. Trimble, Director of Medical Education, Seaside Memorial Hospital, 1401 Chestnut Ave., Long Beach 13, Calif.

The **Fourteenth Annual Symposium on Fundamental Cancer Research** will be held on Feb. 25, 26, and 27, 1960, at the University of Texas M. D. Anderson Hospital and Tumor Institute. It will be devoted to *Cell Physiology of Neoplasia.*

John Lind, M.D., head of the department of pediatrics at Sweden's Carolina Hospital in Stockholm, will be guest speaker at a three-day seminar in **Pediatric Cardiology**, to be held August 16 to 19, 1959, at the University of California conference center at Lake Arrowhead.

The meeting, sponsored by the UCLA School of Medicine and University Extension, is designed for pediatricians, internists, and general practitioners, and will emphasize the diagnostic approach to the patient and current concepts of management.

The Pediatric Cardiology seminar will be followed by seminars in Emotional Problems in Office Practice (August 19 to 23), Internal Medicine (August 23 to 26), and Dermatology (August 26 to 30).

Information and applications may be obtained from the Department of Continuing Education in Medicine, UCLA Medical Center, Los Angeles 24, Calif.

Postgraduate cerebral palsy courses will be offered by **Columbia University**, College of Physicians and Surgeons. The physicians' course will be given Oct. 5 to 23, 1959. The fee is $100. The therapists' and nurses' course will be offered from Oct. 5 through Dec. 4, 1959, inclusive. The fee is $210. A list of scholarship sources will be sent on request.

For additional information, write to Postgraduate Course in Cerebral Palsy, College of Physicians and Surgeons, 630 West 168 St., New York 32, N. Y.

A two-part **postgraduate course in pediatrics** on Clinical and Research Advances in Pediatrics, Sept. 3 to 5, 1959, and on Child Guidance Problems, Sept. 7 to 8, 1959, will be held at Estes Park, Colo.

The tuition fee will be $60.00 for the entire course, or $35.00 for either of the two parts. There is also a $5.00 registration fee.

For further information, write to the Office of Postgraduate Medical Education, University of Colorado Medical Center, 4200 East Ninth Ave., Denver 20, Colo.

The **American Academy of Pediatrics** has recently published a 64 page manual on *Adoption of Children*. Copies of this manual can be purchased from the American Academy of Pediatrics, 1801 Hinman Ave., Evanston, Ill., for $1.00.

This manual has been prepared by the Committee on Adoptions under the chairmanship of Dr. Samuel Karelitz, aided by consultants from the Children's Bureau, the Child Welfare League of America, and the International Social Service.

Books

Technique Chirurgicale Infantile. Bernard Duhamel, Paris, 1957, Masson & Cie, 354 pages. Price Broché 2,800 fr.; cartonné toile 3,500 fr.

Bernard Duhamel has written an excellent book, concise and informative in its presentation of a large number of surgical problems that are encountered in infants and children. In each of the chapters there are excellent summaries of the currently accepted surgical techniques. The diseases treated are those found in the abdominal, cervical, maxilla-facial, and genitourinary regions. A number of miscellaneous items are also presented. Some of the chest diseases in infants and children are emphasized, but for the most part, cardiac problems are omitted. Nevertheless, the book itself is quite useful, since it deals with the most common and, therefore, the most important surgical problems of infants and children.

The illustrations in the text consist of diagrams and line drawings. However, these drawings are numerous and generally quite clear and informative. The book represents an excellent statement of pediatric surgery as it is practiced at L'Hôpital de Saint-Denis. Since the author discusses his own experiences as well as the information in the literature, he speaks with conviction. In addition to reviewing the literature he presents a number of interesting techniques and variations of techniques of his own.

Thomas G. Baffes, M.D.

Correspondence

To the Editor:

I read with concern the advertisement of KYNEX on page 97 of the January issue of the JOURNAL OF PEDIATRICS and would like to bring to your attention four cases of severe toxic reactions occurring in the late summer of 1958.

Three of these cases were pediatric patients of mine receiving recommended doses. The first two were erroneously attributed to penicillin since in both cases 600,000 U. of procaine penicillin was used initially, with Kynex used as follow-up therapy.

Reactions consisted of intense urticaria, conjunctivitis, pedaledema, arthritis, and fever and required 7 to 10 days of Meticorten. . . . Both had received penicillin previously without incident. Several weeks later one-half tablet of Kynex was given as a test dose and immediately vomiting and urticaria occurred in both.

The third case occurred before our suspicions were aroused. This child was given one tablet daily (body weight was 80 pounds) for 12 days. On the last day she developed conjunctivitis and a maculopapular rash which within 24 hours developed into a critical picture of erythema multiforme exudativorum or Stevens-Johnson syndrome, with corneal ulcerations, esophagitis, pneumonitis, and shock. Complete exfoliation occurred. . . . Three months' hospitalization was required and she was fortunate in having only a minor residual keratitis. Of course we were not tempted to prove the etiology in this patient but all consultants felt strongly that it was a sulfonamide intoxication.

The fourth case . . . developed urticaria and arthralgia and conjunctivitis. . . . She had been taking one tablet three times a day for 7 days—a slightly high dosage.

All four of these patients were very fair skinned and the thought occurs that some photosensitivity mechanism might be at play.

My own pediatric cases are drawn from a total of 150 patients to whom I prescribed Kynex.

The research director at American Cyanamid told me he would estimate the incidence of drug rash at 4 per cent. I find no mention of toxicity in the JOURNAL'S advertisement. The implication is that we should fear it no more than the tried and proved triple sulfas. My own incidence of rashes with the latter is certainly no higher than 0.1 per cent.

I feel that more emphasis should be given to the potential toxicity of sulfamethoxypyridazine especially now that Parke, Davis is beginning to market it also. I understand that the latter has done no independent studies but is willing to accept Lederle's research and conclusions. . . .

Sincerely,

JOSEPH F. CRAVEN, M.D.

To the Editor:

. . .Dr. Craven is to be commended for his willingness to bring his experience and ideas to the attention of his colleagues.

His suggestion of a possible photosensitivity mechanism underlying the reactions reported is interesting, although we certainly have no data that would help support this or any other pertinent comment concerning it.

His expressed impression that we have carried out no independent investigations relative to sulfamethoxypyridazine is, however, totally mistaken, and we would wonder how this mistaken idea developed. Dr. Craven could easily have substituted fact for impression here by dropping us a note of inquiry and thereby have avoided doing us a disservice.

We have conducted and are still conducting a variety of appropriate studies.

To date, neither from these studies nor from reports from the field have we had reason to believe that the number, type, and severity of reactions to Midicel (sulfamethoxypyridazine) are significantly different from what have been encountered with other commonly used sulfa drugs. However, since we have not yet marketed a pediatric preparation, it is obvious that our impressions are based largely on an adult population.

In conclusion, we feel sure that Dr. Craven did not mean to give the impression that he was uncritically extrapolating the relatively small number of reactions (some open to question since other drugs known to be associated with similar reactions were used) observed in a sample of 150 patients as a relatively fixed ratio which would necessarily be encountered everywhere in the use of sulfamethoxypyridazine.

Assuring you that we are grateful for your bringing this matter to our attention and allowing us to comment, I am,

Sincerely Yours,

J. K. WESTON, M.D.
Director, Department of Clinical Investigation,
Parke, Davis & Co.

Erratum

At Dr. H. Bickel's request, we would like to make a correction in the editorial on the Foreign Lectureship Program which appeared in the April, 1959, issue of the JOURNAL. Dr. Bickel's rank is Associate Professor of Pediatrics, not Professor of Pediatrics.

Editor's Column

NOT ALONE IN A WILDERNESS

FROM time to time in recent years the JOURNAL has commented editorially on certain matters which it felt had gone quite out of bounds. One of these was the growth and multiplicity of "Fund-for-a-Disease" organizations. As at times it has seemed that we were quite alone in our strictures, it is encouraging to find that others have similar thoughts on the subject. An example is the Presidential Address of Dr. Israel S. Wechsler, of New York, before the American Neurological Association, which was published in the January, 1959, issue of the A. M. A. Archives of Neurology and Psychiatry. To quote:

"May I risk further criticism by saying a few words on the fragmentation of neurology into a variety of popular societies. The trend in recent years to organize lay societies for the popularization of diseases or syndromes, basic knowledge for which is wholly wanting, raises, I fear, the question of scientific integrity. While lay societies may possess a modicum of social and emotional value and give some comfort to the chronically ill, the paramount question is whether popular societies consisting of persons afflicted with lingering illnesses can contribute to scientific investigation and to medical progress? What specific knowledge of causes or treatment can come from lay meetings of sufferers? What are the scientific contributions which have already come out of the highly publicized societies? What neurological or general medical justification is there for holding out vain promises and very generally arousing false hopes which can end only in disillusionment? These questions are not raised or intended to impugn the personal integrity of those who honestly believe that they are doing a public service. . . . Actually there are easier and better ways to obtain financial support, and with less fanfare, certainly now that government and private funds are available for scientific research.

"Quite recently the father of a sick child asked me to sponsor the organization of a popular society of amaurotic family idiocy, a comparatively rare disease, which has, fortunately, begun to disappear. Some years ago I was invited to chair a society of amyotrophic lateral sclerosis. Why not one for tuberous sclerosis? And since there is a society for muscular dystrophy, why not another for muscular atrophies, and still others for all the other myopathies and amyotrophies? Not so long ago a society of myasthenia gravis has come into being, for which there is little rhyme and less reason. There seems to be no end to the popular urge to create more and more societies. I hesitate to mention

multiple sclerosis and cerebral birth palsies and the epilepsies, though there is much, very much, to say on the subject; and I am refraining from further comment to avoid stepping too vigorously on oversensitive toes.

". . . It is my conviction that one can pursue scientific research in private retreats to better advantage than in the open market place."

One must realize that the lay support of "Fund-for-a-Disease" organizations is based in most instances on fine altruistic motives. Unfortunately, the belief has become widespread that all that is necessary to find a solution for medical problems and diseases is publicity to raise money for research. The general public is quite unaware that today there is more money available from governmental and philanthropic sources for medical research than can possibly be used with profit, owing to the lack of qualified investigators; further, that productive research into a disease is dependent upon the ability of the investigator as well as his interest in the particular subject, and that this combination is something that cannot be bought in the market place. The last thing that one would want to do is to destroy public interest in health and medical matters. The real problem is to direct it into paths free from ballyhoo and from organizations whose chief purpose is to raise money for a particular disease without having a clear vision or understanding of how the money collected from the public can be used with profit and not be wasted and frittered away.

B. S. V.